

Section of Proctology

President R W Nevin TD FRCS

*Meeting January 25 1961
(continued from June 'Proceedings' p 520)*

Cases and Specimens

Villous Papilloma of Rectum with Giant Cell Systems

I M P Dawson MD MRCP

Mr J B, aged 78

History: Lower abdominal pain with diarrhoea and passage of mucus for four years. Recently had two separate rectal haemorrhages.

Investigations: Proctoscopy revealed a large papillary tumour in the rectum. A biopsy showed a rectal papillary tumour, probably non-malignant, but no base was included.

Operation: Abdominoperineal resection of rectum.

Pathology: The tumour was a villous papilloma without evidence of invasion of muscle coats and histologically benign. Giant cell system consisting of epithelioid cells and giant cells of Langhans type in a folliculoid pattern without necrosis or caseation were present in submucosa, serosa and adjacent lymph nodes. No acid-alcohol fast bacilli were found.

Comment: Giant cell system, well recognized in large intestinal tuberculosis and Crohn's disease, may also occur in association with tumours of the intestinal tract (Symmers 1951, Gresham & Ackerley 1958). They probably represent a reaction to a product of neoplastic growth or to breaking down tumour cells.

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Primary Actinomycosis of the Rectum

B C Morson DM

J C, male, aged 59. Bus driver for many years.

10.1.60: Admitted under Mr C Naunton Morgan at St Mark's Hospital with a history of twenty years' increasing constipation. In 1957 he

attended Wembley Hospital where a biopsy of the rectum was taken. The patient subsequently attended regularly for digital dilatation.

No history of dental caries. He has never worked in an agricultural occupation, but looked after two ponies for some time when he was about 14 years of age. Symptoms have recently become more severe with some hypogastric pain. He has his bowels opened every two or three days, always with tenesmus.

Examination under anaesthesia and rectal biopsy: There is an indurated ridge encircling the rectum just above the anorectal ring, with some narrowing of the lumen but no mucosal ulceration. The pathological changes appear to be intra- and extramural. Frei test negative.

Biopsy report: Section shows numerous fragments of rectal mucosa, submucosa and deep muscle layers. All these fragments show some increased intramural fibrosis but there is no ulceration of the mucous membrane. One piece of tissue contains a well-defined abscess cavity filled with pus and colonies of actinomyces (Fig 1).

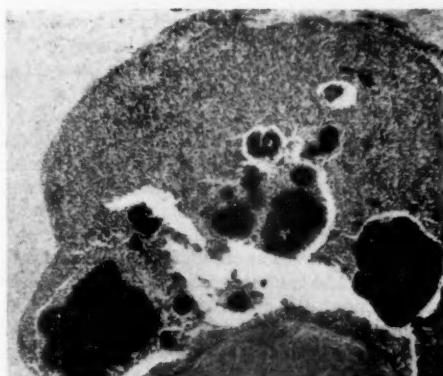


Fig 1 Section shows an abscess cavity containing pus and colonies of actinomyces; the wall is composed of avascular fibrous tissue (PAS $\times 20$)

Treatment: Ten-day course of Achromycin 250 mg four times a day and potassium iodide.

May 1960: No symptoms. No stricture present and no induration.

August 1960: Sigmoidoscopy normal to 15 cm.

Comment: Actinomycosis of the rectum is rare. According to Cope (1938) there are two varieties: one in which the disease is the result of spread from an ileocecal actinomycosis, and another in which the infection may be regarded as primary in the rectum. Clinical and radiological studies of this patient failed to demonstrate actinomycosis elsewhere including the ileocecal region. Most reported cases of primary rectal actinomycosis have had anal or anorectal fistulae, but these were not present in this patient.

The response to treatment with Achromycin was satisfactory and probably there will be no recurrence.

Actinomycosis should be included in the differential diagnosis of smooth submucous strictures of the rectum. A rectal biopsy supported by other laboratory tests will enable the pathologist to make the distinction between anaplastic carcinoma with extensive submucous spread, carcinoma of the prostate invading the rectum, lymphogranuloma venereum, and syphilitic gumma of the rectum, all of which may have a similar clinical presentation.

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Multiple Metastases in Muscle from Adenocarcinoma of Rectum J F Newcombe FRCS (for F A Henley FRCS)

H F, a retired clerk, aged 69, underwent an abdominoperineal resection of the rectum in July 1957, for a large adenocarcinomatous ulcer 3 cm from the anal margin, infiltrating all coats and involving one adjacent lymph node (Duke's C.1). He was well until October 1960 when swellings appeared in the left groin and buttock. One month later a painless swelling of the left calf was observed.

On examination: The right lower limb shows shortening and muscle-wasting from an old unreduced congenital dislocation of the hip. On the left side are 3 lesions (Fig 1): (1) Two firm masses in the left gluteal region. Both appear to be in the substance of the gluteus maximus muscle. The medial is fixed to the sacrum and ilium; the lateral is more mobile. (2) A large diffuse mass with dilated vessels on the surface in the muscles

of the left calf and extending into the popliteal fossa. The maximum circumference was 17.5 in., as compared with 12 in. on the right. (3) An enlarged, hard, superficial left inguinal lymph node.

Röentgenography showed no evidence of metastases in the chest, in the pelvis, vertebral column or skull. There was no sign of invasion of the bones of the left lower limb.

Biopsy of the left inguinal lymph node showed metastatic carcinoma similar histologically to the original lesion.

Comment: Distant metastases from carcinoma of the rectum and sigmoid colon are common. They have been reported in a variety of sites, including thyroid, adrenals, breast, penis, inferior vena cava and spleen.

Metastasis to the skeletal system has also frequently been reported. However, there appears to be no previous reference to metastasis in skeletal muscle without simultaneous involvement of bone.

Two extensive series may be quoted: Bacon (1940), in a review of 366 post-mortem cases, found that 126 showed distant metastases. Of them 67 (practically one-half) showed deposits in the lungs. Fifteen showed bone metastases. The remainder were found in various sites but none was reported in muscle.

Similarly, Mayo & Schlicke (1942) reviewing



Fig 1 Showing the diffuse mass in the left calf. Note the absence of lymphædema

334 cases, do not describe such an instance, whilst the incidence of skeletal metastases was only a little over 1%—much less than that found by Bacon.

The interesting feature of this case is the presence of metastases in limb muscles without concomitant involvement of bone and without radiographically demonstrable lesions in the lungs. The mode of spread is uncertain, but it seems that the blood stream is the likely route, with involvement of the superficial inguinal and popliteal lymph nodes occurring secondarily. This implies that the lungs have been by-passed, or have permitted the passage of malignant cells without becoming involved.

Retrograde spread of the growth along venous

or lymphatic pathways is unlikely, particularly in the absence of oedema in the limb.

A possibility is that these lesions in muscle are primary tumours and not secondary deposits. This has not been tested by drill biopsy, but it seems improbable that they should appear simultaneously with proven metastases in the superficial inguinal lymph nodes.

Treatment with a new antimetabolic preparation—5-fluoro-uracil—is proceeding, but it is too early to determine the response.

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Meeting February 22 1961

Short Papers

Resection of Carcinoma of the Colon in the Presence of Obstruction

by C Patrick Sames MS FRCS (Bath)

For many years surgical teaching has emphasized the dangers of immediate resection and anastomosis of large bowel in the presence of obstruction, due to the risk of peritonitis.

Suture of the large bowel in obstruction is hazardous for the following reasons: (1) Increased bacterial content due to obstruction. This, however, only applies to that part of the bowel 'proximal' to the obstruction. (2) The nature of the blood supply to the colon with its long marginal artery and relatively few vasa recta. The blood supply varies with the age and cardiovascular condition of the individual. (3) Sacculation of the bowel due to the muscular tenuæ, which makes accurate suturing more difficult. (4) The presence of appendices epiploicae. (5) The presence of diverticula. (6) The nature of large bowel contraction by powerful mass action, as opposed to peristalsis. (7) The solid nature of the stool.

The classical three-stage procedure of establishing a proximal colostomy, resecting the growth, and later closing the colostomy, involves the patient in a lengthy illness. Often the interval between the colostomy and the radical removal is protracted, because of post-operative complications, such as wound sepsis or chest infections; or because of administrative errors, such as shortage of beds or operating time; or sometimes delay in acquiescence by the patient. Most surgeons have

experienced the disappointment of finding that a carcinoma, previously judged to be operable, has become too advanced for curative resection or even palliation. Admittedly occasional cases which look inoperable may become resectable when secondary infection and oedema have subsided after the colostomy. It must be every surgeon's desire to remove a resectable carcinoma as soon as it is discovered.

The standard procedure for the *right* side of the colon is a preliminary ileotransverse colostomy, but it is accepted that liberties can be taken more safely on the right than on the left. In rare cases of closed loop obstruction where the ileocaecal valve has remained competent, resection and direct anastomosis between ileum and transverse colon is safe, as collapsed bowel is on both sides and proximally it is the small intestine which is being sutured. In obstruction of a lesser degree where the ileocaecal valve may be incompetent resection can be done safely. If there is anxiety, resort can be made to a Muir's procedure (1947) of side-to-side ileotransverse colostomy with a temporary vent at the proximal end of the transverse colon. The subsequent faecal fistula closes without difficulty. Many surgeons are even prepared to dispense with this, if the obstruction is not too gross.

When dealing with obstruction in the *left* colon the alternative to the three-stage operation before the antibiotic era was the Paul-Mikulicz procedure, where the subsequent extraperitoneal closure of the double barrelled colostomy sometimes reduced the stages to two. This is, however, only practicable in cases of minimal obstruction,

as it does not permit a wide resection of the lymphatic field.

With the aid of antibiotics intraperitoneal suturing has become safer, but nevertheless immediate anastomosis in the presence of obstruction, without preliminary bowel preparation, is not to be recommended. With the help of chemotherapy, the three stages of the operation can occasionally be reduced to two if closure of the colostomy is simultaneous with the major resection. Brooke (1955) advises making the colostomy near to the lesion, so that at the second stage the growth and the colostomy can be resected as one, and the operation completed by end-to-end anastomosis. If the colostomy is not resected with the growth, care should be exercised when undertaking simultaneous closure that there is, in fact, sufficient blood supply to the intervening part of the colon between the two anastomoses. Tragedy can sometimes occur if this necessity is overlooked.

Until now, except for the Paul-Mikulicz procedure, there has been no satisfactory method of removing the growth at the first surgical intervention. This paper proposes to show that immediate resection of a carcinoma of the left colon in the presence of obstruction is, in selected cases, a safe procedure. The underlying principle is that the growth, with its field of lymphatic spread, is excised, the proximal bowel brought out as a terminal colostomy, and the distal bowel closed and dropped back (as in a Hartman's operation for carcinoma of the rectum). At a second operation - at a suitable time - the bowel is reconstituted.

Technical Considerations

The resection of a carcinoma of the obstructed left colon is not to be undertaken lightly or by the occasional surgeon, and should be reserved for selected cases. The patient should not be excessively obese. The growth should be mobile and easily resectable.

Handling of the distended coils of bowel is easier where the ileocaecal valve has become incompetent, resulting in partial decompression of what was formerly a closed loop obstruction in the colon.

The operation is probably best reserved for cases where the growth is at or above the peritoneal shelf, for if the rectum is mobilized at the first operation difficulty in restoring continuity follows. The temptation to open the lines of cleavage in the hollow of the sacrum must be resisted, though there is no objection to making the resection at the level of the peritoneal reflexion.

Decompression of the bowel by a sucker, which is often disappointing, is probably best performed outside the abdomen after the bowel, with its

growth, has been exteriorized, as contamination is less likely.

The temporary colostomy should be sited at the upper end of the paramedian incision, as it facilitates dissection at the second operation. Reconstitution is undertaken when the patient's health is optimal; the lethal cancer is away, and restoration is an 'operation of convenience'.

To prevent difficulty in finding the distal end of the colon, a black suture may be used to mark it and the rectum is packed with gauze prior to the second operation.

Although my experience of this manoeuvre is limited (Sames 1960) I believe the possibility should be borne in mind as an alternative to the standard operation. It removes an obstructive growth at the first intervention, yet entails no suturing of distended bowel. Admittedly degrees of obstruction vary, but where things are favourable a plea is made for this procedure. It not only reduces morbidity, but may lengthen survival.

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Exfoliative Cytology of the Colon

by J I Burn MB FRCS (*London*)

Introduction

Early attempts at cytological studies in colonic disorders were based upon the examination of rectal and sigmoidal discharges (Hunter & Richardson 1947, Wisseman *et al.* 1949, Blank & Steinberg 1951). The degree of accuracy in demonstrating malignant cells under such conditions was not conspicuous. In 1952 Bader & Papanicolaou published a report on the use of cyto-diagnosis in carcinoma of the colon, in which they examined diagnostic washings from the large bowel and were able to identify cells exfoliated from the surface of malignant neoplasms. The same authors also described the normal cytology of the colon, and stressed the importance of adequate cleansing before examination.

Despite this interest, exfoliative cytology, which has been of considerable value in the diagnosis of malignancy in other organs, has been largely neglected with respect to colonic disorders. Presumably this is due to the difficulty in obtaining specimens sufficiently free from faecal contamination and in isolating a few cells from a large volume of colonic washings. In the few reports available where a genuine attempt has been made to overcome these difficulties impressive diagnostic accuracy has been claimed (Rubin *et al.* 1953, Galambos & Klayman 1955, Ebeling & Little 1957, Raskin *et al.* 1959).

Technique

Mr R A Sellwood and I have had opportunity to study the techniques employed in exfoliative cytology of the colon, and to satisfy ourselves with the appearance of the malignant cells we might expect to find, two preliminary investigations were undertaken. A series of smears was made on glass slides from the surface of cancers of the large bowel immediately after resection. After fixation these were stained by either a Papanicolaou or May-Grünwald-Giemsa technique. Cold Ringer-Locke solution was run through the lumen of resected colons and collected, a centrifuged deposit being smeared on to slides. Fig 1 illustrates a cluster of malignant cells obtained from such a washing. It seemed reasonable to suppose that comparable clusters of malignant cells could be obtained from diagnostic colonic washings in patients with cancer of the large bowel.

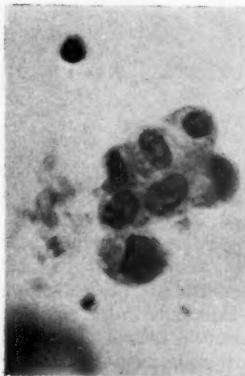


Fig 1 Malignant cells from intraluminal washings of a resected carcinoma of transverse colon. $\times 600$

As emphasized by Oakland (1957) and Raskin *et al.* (1959) it is important that the diagnostic washings obtained should be free from faecal and other detritus. This necessitates laborious toilet of the colon, and if this is not done cytodiagnosis is virtually impossible because of the amount of debris on the slides. Our preparation is similar to that advised by Raskin and his colleagues (1959). In all patients, clear fluids only are allowed by mouth for thirty-six hours before the examination. An aperient may be given the night before, but this varies depending on the suspected underlying lesion. The essence of the preparation, however, is thorough cleansing of the large bowel with repeated saline enemas and rectal washouts, until the returned fluid on two consecutive occasions is clear of all solid matter and has only a faint discolouration. When adequate cleansing has been obtained, the patient is left for one hour before the diagnostic washing.

The patient is placed in the genupectoral position and sigmoidoscopy performed. When the lesion is beyond the sigmoidoscope cytodiagnosis has most to offer, and we have only occasionally carried it out for rectal lesions. A long colonic tube is inserted through the lumen of the sigmoidoscope and beyond. This tube has an inflatable balloon which helps to retain its position and ensures that all the returning fluid passes through the tube. The sigmoidoscope is withdrawn and 600 ml of cold Ringer-Locke solution is introduced slowly through the tube. The patient is positioned carefully to allow contact of the solution with all parts of the colonic mucosa beyond the balloon. This part of the procedure may take several minutes and should not be hurried. The patient is turned on his left side for the return of the fluid, which is siphoned through the tube and collected in an ice-cold chamber, after filtration through a wire mesh filter which retains all particles of more than 140μ in diameter. Immediately after collection the fluid is removed for examination.

The isolation of cells from a large volume of fluid is a recognized problem (Seal 1956); the usual practice is to centrifuge and examine the sediment. Satisfactory preparations may be obtained, but many slides may require screening before an opinion can be given because of the sparse cellular deposit, and malignant cells may be missed. As an alternative method we have used a membrane filter technique with a 5μ Millipore filter (Cameron & Thabet 1959). These filters are thin porous membranes and contain millions of evenly distributed pores of precise size which occupy over 80% of the total filter volume. Particles removed from the filtered fluid lie directly on the filter surface and are available for examination. The diagnostic washing is passed through the membrane at a filtration pressure of 5 mm mercury. The filter surface becomes loaded with cells after about 30 ml have passed through. Filtration of too much fluid must not be attempted. Immediately after filtration, 10 to 20 ml of tertiary butyl alcohol is poured into the filter holder and the vacuum source disconnected. After ten minutes the alcohol is drawn through the filter with gentle suction and the filter removed with forceps. It may be placed in fixative or stained at once. The filter membrane becomes transparent when cleared with xylene so that the cellular deposit can be examined microscopically. This method facilitates the concentration of a few cells from a large volume of fluid and ensures that they can all be examined.

Colon Cytology

The extreme simplicity of the normal cytology of colonic washings makes the presence of atypical cells immediately obvious to the observer. Ex-

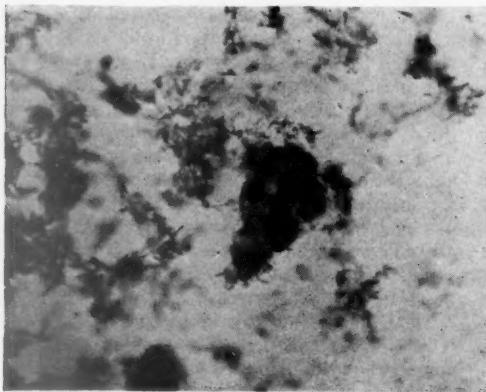


Fig 2 A cluster of normal epithelial cells from the colon. $\times 675$

foliated columnar and goblet cells are readily recognizable, as are squamous cells presumably introduced by the sigmoidoscope from the epithelium of the anal canal. Fig 2 illustrates normal epithelial cells. When the colon is inflamed as in diverticulitis or ulcerative colitis the exfoliation of epithelial cells is increased. It must be remembered that normal epithelial cells are liable to distortion leading to a bizarre appearance, particularly in severe inflammatory lesions of the bowel mucosa.

Malignant cells from cancer of the large bowel tend to exfoliate in clumps, a feature which assists their recognition. Such cells are larger than the normal epithelial cell, and exhibit pleomorphism of nuclear size, shape and chromatin content within any given clump of adenocarcinoma cells. The recognition of the cancer cell has been much discussed (Papanicolaou 1954, Sriggs 1960), but it is usually not too difficult in colonic cytodiagnosis. Figs 3 and 4 are examples of malignant cells from diagnostic colonic washings.

Discussion

In a small series of 45 cases we have included a variety of lesions, and are satisfied that malignant cells may be isolated and identified and that all of the colon is open to investigation.

There has been increasing awareness during the past decade of the need to prevent the dissemination of cancer cells at surgical resection (Morgan & Lloyd-Davies 1950, Cole *et al.* 1954, Smith *et al.* 1958, Economou *et al.* 1959). If this is to be achieved, greater diagnostic accuracy before operation becomes essential so that vessel ligation and mobilization of the tumour may be performed with the minimum of handling of the cancer. Reliable cytodiagnosis is of particular value in

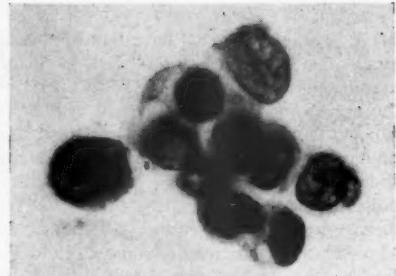


Fig 3 A group of malignant cells from diagnostic washings in a patient with carcinoma of the sigmoid colon. $\times 825$

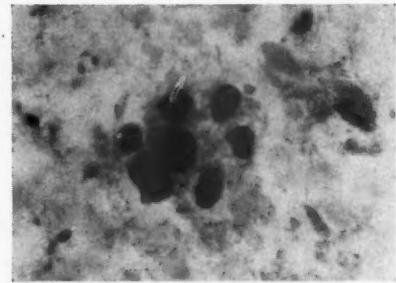


Fig 4 Malignant cells on a Millipore membrane filter. $\times 675$

the following: (1) Identification of malignant strictures of the colon, especially in the sigmoid region. (2) Filling defects of the caecum. (3) Where premalignant conditions such as polyposis or chronic ulcerative colitis are known to exist. Malignant change may occur in these patients and may be difficult to recognize in the early stages by conventional diagnostic methods. (4) When local recurrence is suspected in a patient who has had a previous resection for malignant disease of the colon.

Admittedly the investigation has its limitations. The preparation is tedious, and there remains the difficulty of recognition of the cancer cell.

Acknowledgments: I am greatly indebted to the members of the Surgical Staff of the Hammersmith Hospital for permission to carry out this investigation on patients under their care.

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A Summary of the Clinical Features of 100 Cases of Benign Lymphoma of the Rectum and Anal Canal

by J S CORNES BSC MB DCP, M Helen Wallace BSC
 and B C MORSON DM (London)

Benign lymphomas of the rectum and anal canal are small localized overgrowths of the lymphoid follicles normally found here. They are not common, and a pathologist working in a busy hospital will be fortunate if he sees more than two or three examples in his lifetime. These tumours present as sessile or pedunculated polyps, which when large enough to be seen are often a source of difficulty in diagnosis. In the series of 70 cases reported by Helwig & Hansen (1951) about one-half were originally diagnosed microscopically as malignant tumours of lymphoid tissue.

The first patient seen at St Mark's Hospital in 1926 was a 6-year-old girl who presented with a sessile polyp in her rectum. A rectal biopsy was reported as lymphosarcoma, and an abdomino-perineal excision of the rectum was performed. When the operation specimen was examined by Dr C E Dukes, he was struck by the follicular pattern of the tumour and its situation entirely within the submucosa. In the next few years several similar cases were seen, and in 1934 Dr Dukes in a paper describing 3 cases expressed the opinion that the tumours were benign and could be cured by simple local removal. By May 1960, excluding cases of lymphoid hyperplasia associated with ulcerative colitis or granular proctitis, 100 cases of benign lymphoma had been seen at St Mark's Hospital.

These tumours occurred slightly more frequently in males, and were found in all age groups, ranging from 5 to 81 years of age, but were most common in the third and fourth decades. Haemorrhoids were found in over a third, and carcinoma of the rectum in 7. In 41 cases no associated pathological conditions were found and in this

group the most common presenting symptoms were rectal bleeding, prolapse, constipation, and anal pain or tenderness. In the majority the symptoms had been present for one year or less, but in 2 cases for five years and ten years respectively.

On proctoscopy 143 polyps were seen in the 100 patients examined. Over two-thirds were sessile, and less than one-third pedunculated. In 78 patients the polyps were single, and in 22 two or more were found. Over 80% of the polyps were in the lower third of the rectum, or at the mucocutaneous junction of the anal canal. Their distribution was random around the bowel circumference, and there was no predilection for any quadrant.

Treatment

In 93 cases the polyps were removed by simple excision, and in the remaining 7 cases the polyps were removed with specimens containing carcinomas of the rectum. Two-thirds of the polyps were apparently incompletely removed, as lymphoid tissue extended to the resected edges of the specimens. The smallest polyp measured 0.3 cm in diameter, and the largest 3.8 cm, whilst three-quarters were 1.5 cm or less. In 98 cases the tumours were apparently confined to the mucosa and submucosa; muscle coat invasion was seen in 2 cases. The pathological features have been considered in detail elsewhere (CORNES *et al.* 1961).

Seventy-three patients have been followed-up for more than one month after treatment, 35 for more than five years, and 18 for more than ten years. Despite the frequency of incomplete removal local recurrences were found in only 5 patients, and none has developed a malignant tumour of lymphoid tissue. Although this follow-up leaves much to be desired there is no evidence that these tumours become malignant, and the advice given by Dr Dukes in 1934 that simple removal is the only treatment required is confirmed.

Acknowledgments: Appreciation is expressed to the Consultant Staff of St Mark's Hospital, and to Members of the Section of Proctology who sent specimens to the Pathology Department, for access to clinical records, and for help with the follow-up study. The work was supported by a grant to the Research Department from the British Empire Cancer Campaign.

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Syphilitic Ulcers of the Anus

by R M Hollings FRCs FRACS (London)

This paper is based on the cases of syphilis affecting the anus seen in the Out-patient Department of St Mark's Hospital between 1932 and 1960. The objective in reviewing these cases is: (1) To illustrate some of the diagnostic features of anal syphilis. (2) To emphasize the importance of homosexuals as a reservoir of infection at a time when the overall incidence of the disease is falling (Ministry of Health 1960). (3) To add to the rather sparse literature on the subject. 'Discussion of primary ano-rectal syphilis as found in the literature is very meagre and incomplete and descriptions are inaccurate' (Martin & Kallet 1925). To some extent this criticism is applicable to 1960.

The most recent review of the subject to come from St Mark's Hospital is that of 55 cases seen at the hospital in the seven years 1882–1888 (Goodsall & Miles 1900) (Table 1). The majority of these are assumed to be secondary stages as Goodsall states elsewhere in his book that he had seen only one anal chancre at both St Mark's and the Gordon Hospital. Chancres of the anus were more commonly found in women (Lockhart-Mummery 1914). To-day the majority of cases are in men.

Table 1

Summary of 55 cases of anal syphilis (Goodsall & Miles 1900)
St Mark's Hospital Out-patient Department 1882 to 1888

		Average age	Range
Males	37	31 years	18–57 years
Females	18	24 years	2–42 years
<i>Principal clinical features:</i>			
Mucous patches in anal region		33	No. of cases
Ulceration in anal region		12	
Syphilitic fissures		6	
Primary anal chancre		1	
Ulcer of rectum		1	
Gumma of both sides of anus		1	
Gumma of one side of anus with fistula		1	
<i>Secondary clinical features:</i>			
Enlarged inguinal lymph nodes	43		
Primary sore still present	29		
Rash	15		

This series is of a comparable number of cases spread over a longer period (Table 2). It is not possible to assess with accuracy the numbers of primary lesions as the clinical notes were frequently not explicit on this point, however it is certain that chancres form a majority of cases seen in recent years. The frequency of enlarged inguinal nodes, a watery discharge from the ulcer and the presence of a rash make these valuable diagnostic signs, as also noted in the earlier series.

Investigations carried out included dark ground microscopy and the Wassermann reaction. The

Table 2

Summary of 65 cases of ano-rectal syphilis (present series)
St Mark's Hospital Out-patient Department 1932–1960

	Average age	Range
Males	57	31·6 years
Females	8	31·5 years
<i>Principal clinical features:</i>		
Condyloma		29
Ulcer		31
Fissure		13
<i>Associated clinical features:</i>		
Enlarged inguinal lymph nodes		42
Watery discharge from anal lesion		21
Anal tags		11
Rash		9
Genital lesion present at some time		11
<i>Presenting symptoms in current series:</i>		
Pain on defecation		24
Lump in the anal region		14
'Piles'		9
Irritation		7
Bleeding		6
Discharge		5
'Sore' on anus		3
Diarrhoea		1

former method was not employed in the earlier years of the survey and all 3 cases with a negative Wassermann reaction subsequently became positive. Where biopsy confirmed the diagnosis, it usually meant that the tag had been excised in the mistaken belief that it was a non-specific lesion.

It was rare for the general practitioner referring the patient to suspect the diagnosis. By contrast 58 out of the 65 cases were correctly diagnosed on their first visit to the clinic.

The occupations of the patients show a higher proportion of actors and musicians than this group would represent in the community (Nicol 1960).

The annual incidence of cases reflects the general level of syphilis in the community with its post-war peak and the rise in the last twelve months (Fig 1).

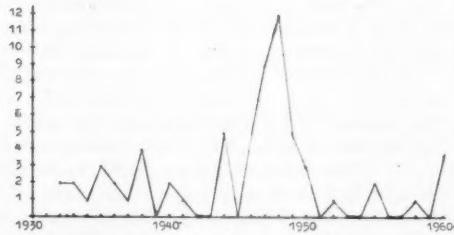


Fig 1 Graph showing annual incidence of cases

I am indebted to Dr W N Mascall of the St Paul's Hospital Clinic for his figures for 1960 to illustrate the problem as it relates to homosexuals (Table 3). Despite the progressive fall in the incidence of syphilis, there does appear to be an increase in the disease among homosexuals who constitute a rising menace in the spread of infec-

tion. Exogenital lesions are being found in them in greater numbers (Degos 1958, Hecht 1957).

Table 3

Summary of 67 cases of syphilis at St Paul's Hospital, Endell Street Clinic (1960)

Homosexuals:	Active	17	53 (79% of total cases)
	Passive	31	
	Active and passive	5	
Lesions in homosexuals	Anal chancres	14	
	Penile chancres	12	
	Secondary syphilis	16	
	Latent syphilis	11	

A greater awareness of anal syphilis must precede earlier and more accurate diagnosis. This will lead to earlier and more effective therapy. Prevention can be achieved by better education of the public and careful follow up of contacts.

Acknowledgments: My thanks are due to Dr Basil Morson, Director of the Research Department, and the Consultant Staff of St Mark's Hospital; also to Dr W N Mascall of St Paul's Hospital, Dr C S Nicol of St Bartholomew's Hospital and Dr R R Willcox of St Mary's Hospital.

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Necrotizing Colitis

by M J Killingback FRCS
and K Lloyd Williams MChir FRCS (London)

Mr M J Killingback

Gangrene of the colon is a rare condition and was first described by Lauenstein in 1882 when he reported a case of infarction affecting the transverse colon. More common causes of gangrene affecting the large bowel are strangulation produced by intussusception, volvulus or hernia.

This paper introduces seven cases of a fulminating gangrene affecting the large bowel. A description has not been previously reported in the literature.

Clinical Features

The patients were admitted to the Central Middlesex, St Mark's, Westminster and Woolwich Memorial Hospitals between September 1957 and March 1960. There were 5 females and 2 males aged 56 to 78 years. Their illness was severe, causing the death of 3 patients.

Their symptoms began with a sudden onset of severe abdominal pain, usually accompanied by peripheral cyanosis and collapse. Abdominal distension was noted in 5, 4 were diagnosed as acute pancreatitis until the serum amylase estimations were carried out, 2 others were thought to have generalized peritonitis and one other, intestinal obstruction with strangulation.

Laparotomy

Laparotomy was undertaken soon after admission in all. On opening the peritoneal cavity a foul odour was noted. There were large amounts of turbid free fluid. The most striking feature was the presence of patches of green gangrene scattered over the surface of the large bowel. The situation of these areas varied considerably from case to case (see Fig 1). This gangrene was associated with an intense inflammation of the serosal surface accompanied by marked oedema in the bowel wall, mesentery and related retroperitoneal tissues.

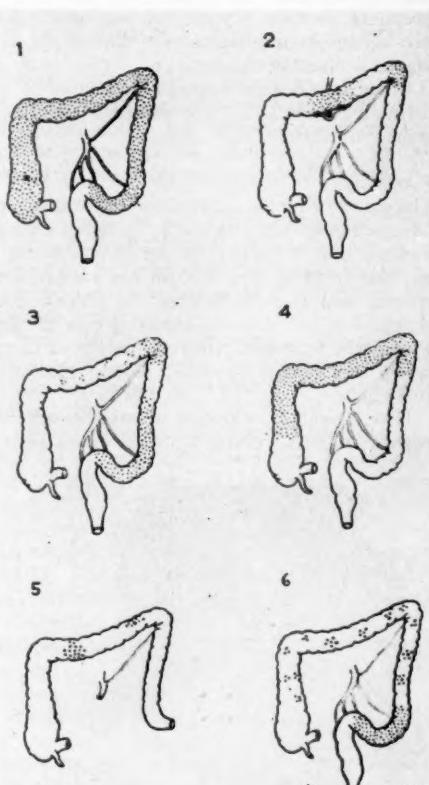


Fig 1 The dotted areas show the distribution of the gangrene on the serosal aspect of the bowel in 6 of the 7 cases



Fig 2 The enormous dilatation of the inflamed sigmoid loop with small patches of gangrene on the surface and affecting similarly the splenic flexure and transverse colon

Some of these features are shown in Figs 2 and 3.

The mesenteric vessels were adequately examined in Cases 2, 3, 5, 6 and 7, and found to be pulsating. In Case 6 some epicolic vessels were divided deliberately to assess the blood supply and vigorous bleeding occurred.

Cases 1 to 6 were treated by resection of the diseased bowel. Case 7 was treated by transverse colostomy alone.

Pathology

The gangrene on the external surface of the colon has been described as a patchy irregular change. Examination of the mucosa, however, revealed a startling contrast. The mucosa was swollen with oedema and was black-brown in colour. This change was uniform and extended over a much wider area than that affecting the serosa of the bowel. The mucosa was intact without ulceration (see Fig 4).

Histological examination showed a selective necrosis of the bowel wall which almost exclusively



Fig 3 A more confluent area of gangrene on the transverse colon which is intensely congested

affected the mucous membrane. In this layer the tubular glands had disappeared leaving in some areas only ghost outlines. The submucosa was oedematous and filled with inflammatory cells. The muscle layers were largely intact.

Fig 5 shows the characteristic histological appearances. There was no histological evidence in the bowel wall or mesentery of vascular disease or vascular obstruction.

Case Report

Case 7 A male, aged 68, who had suffered from diabetes mellitus for seven years. He had also complained of diarrhoea for twelve months prior to this admission to hospital. On this occasion he complained of severe generalized abdominal pain of sudden onset accompanied by vomiting.

On examination: He appeared very ill with peripheral cyanosis and was said to have impending peripheral circulatory failure. His abdomen was tender and generalized rigidity was present. On rectal examination there was a mass palpable at the limit of the examining finger. He was resuscitated with intravenous fluids and laparotomy was undertaken. Foul-smelling fluid was



Fig 4 The diffuse gangrene of the mucosa showing a swollen, non-ulcerated appearance



Fig 5 Necrosis of the tubular glands with intense hyperaemia and polymorphonuclear infiltration of the submucosa. H and E $\times 35$

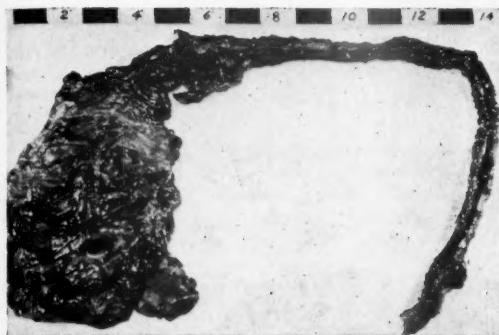


Fig 6 Subtotal colectomy specimen showing extensive stricture formation which developed distal to the transverse colostomy, corresponding exactly to the segment of colon previously affected by the gangrene

found in the peritoneal cavity and the colon appeared inflamed with small green flecks of gangrene scattered over its surface from the mid-transverse colon to the sigmoid colon. No resection was undertaken, but a transverse colostomy was constructed with colon which appeared normal. The abdominal wound was closed and the colostomy opened immediately. The mucosa of this colostomy appeared black and oedematous, the changes being similar to those shown in Fig 4.

The patient made a slow but steady recovery and subsequent examination of the mass in the rectum revealed an adenocarcinoma at 13 cm. Two months after his original admission to hospital this tumour was removed when a restorative resection was undertaken. At operation the colon previously affected by the gangrene was contracted and stenosed. It was left *in situ* as was the transverse colostomy. The patient's recovery from this operation was rapid. He was readmitted three months later and subtotal colectomy and an ileosigmoid anastomosis performed. The specimen is shown in Fig 6; Fig 7 shows the atrophy of the mucous membrane and the extensive fibrosis of the submucosa.

Discussion

These 7 patients have suffered from the same disease which has varied in its distribution and extent throughout the colon. The mucosa appears to suffer the greatest disorganization, and in all cases this is associated with an intense inflammatory reaction in the submucosa. In some cases the necrosis was full thickness, and perforation would have seemed inevitable.

In Case 7, however, where resection was not carried out, perforation of the small flecks of necrosis as seen on the bowel surface did not occur. This case has provided an opportunity to examine the natural history of the disease. The mucosa in the less-affected area such as the transverse colostomy recovered completely. Elsewhere mucosal atrophy and extensive submucosal fibrosis occurred producing an extraordinary stricture.



Fig 7 Extensive submucosal fibrosis and atrophy of the mucous membrane. H and E $\times 3$

Mr K Lloyd Williams

Aetiology

The dramatic onset of gangrene suggested a vascular origin, but we had to revise our diagnosis when no evidence of infarction was found histologically in either the resected or autopsy specimen.

When considered more critically the cases have features which differ from those of infarction:

- (1) *There was no haemorrhage* into the bowel lumen or peritoneum; such haemorrhage is common in infarction.
- (2) There were no predisposing factors to infarction such as ischaemic heart disease, cardiac arrhythmias, portal hypertension or recent abdominal surgery.
- (3) *Our cases were more dramatic in onset and more virulent in nature.* Most of them were in hospital within fourteen hours of the onset of their disease, and all were operated on shortly after admission as acute emergencies. Infarction is often insidious: McCort (1960) describes 3 cases where operation was not performed until the second, third and twenty-second day.
- (4) Our patients were cyanosed and toxic and 3 were in peripheral vascular failure, whereas an acute infarct usually presents the picture of concealed blood loss.
- (5) The patchy, greenish gangrene of serosa with contrasting uniform, black, non-ulcerated mucosa is unlike the swollen, turgid, red bowel, oozing blood-stained serum, of haemorrhagic infarction.

Isolated gangrene of the large bowel is rare and we have only found 27 cases in the literature. However, owing to the kindness of Dr J K Rijs-

bosch (1958), Dr J J McCort (1960), Dr H L D Duguid (Blair & Duguid 1960), Mr G. E. Mavor (1959) and Mr C I Cooling (Cooling & Protheroe 1958) we have secured the pathological material from 7 of these and have compared them with our material. There are similarities, in that the mucosa bears the brunt of the ischaemia and shows more necrosis than the other layers of the bowel wall. Ulceration of the mucosa is common in infarction but has not occurred in our cases. Also in infarction there is usually thrombosis in small vessels within the bowel wall.

We considered the possibility of fulminating ulcerative colitis, staphylococcal enteritis, and pseudomembranous enterocolitis, but there are many clinical and pathological differences and our cases do not fit into any of these groups. This did, however, lead us to consider infection as a possible aetiology. There were several factors which made this a possibility - the intense inflammation of the serosa as seen at operation, the remarkable oedema of the mesentery and retroperitoneal tissue, the patchiness of the gangrene and histologically the intense inflammatory response with polymorphonuclear infiltration of the mucosa.

We therefore performed Gram stains of the histological material. We were surprised to find large numbers of organisms present in all 6 sections examined. The organisms were largely Gram-positive rods (Fig 8). Their distribution was mainly in the deeper parts of the mucosa, at the site of the maximum polymorphonuclear inflammatory response (Figs 9 and 10).

Gram sections of all our cases have been examined by Dr Alan Gray of the Central Middlesex Hospital, who is of the opinion that these organisms morphologically appear to be clostridia and most probably *Clostridium welchii*.

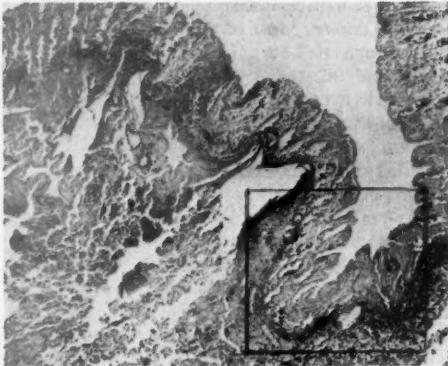


Fig 9 Case 6 Showing mucosal necrosis, gross oedema of submucosa and intense polymorphonuclear infiltration of submucosa. H and E $\times 35$

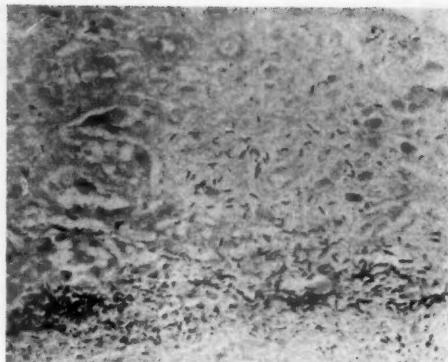


Fig 8 Case 2 Showing large numbers of Gram-positive rods in the deeper parts of the mucosa. Gram stain $\times 350$

Their presence in the tissues raises the question of whether they are primary invaders causing necrosis of tissue or secondary invaders of tissue already dead from some other cause.

We believe that they are primary invaders; this belief is supported by the presence of uniform, heavy colonization in the deeper layers of the mucosa, by the intense polymorphonuclear reaction, which is particularly marked around the colonies of bacteria, and by the contrast with Gram studies of infarcted material where infection must be assumed to be secondary. Here we were struck by the paucity of organisms which were mixed in type, mainly Gram-negative cocci and rods, and were situated almost exclusively in the superficial layers of the mucosa.

The concept of clostridial infection of the alimentary tract is not a new one. It causes diseases in animals (such as braxy, enterotoxaemia and lamb dysentery) and is responsible for occas-

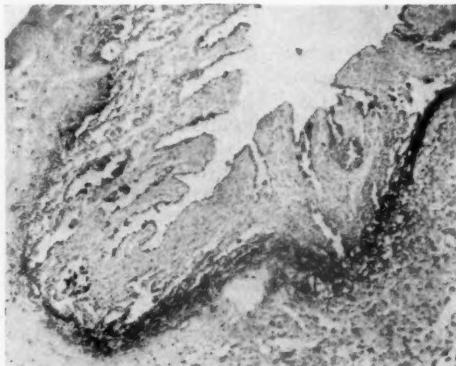


Fig 10 Case 6 Higher power view of area shown in Fig 9, showing relation of organisms in submucosa to polymorphonuclear infiltration. Gram stain $\times 90$

ional wound infections following operations on the large bowel in man. Zeissler & Rassfeld-Sternberg (1949) described a *Clostridium welchii* infection of the small bowel occurring in North Germany which they called enteritis necroticans. Fethers (1959) reported the only case of this disease in the literature from this country. He described gangrene of the jejunum which complicated haematemesis from a duodenal ulcer. The patient suddenly developed signs of a peritonitis shortly after admission and at laparotomy free fluid with a foul odour was noted and a 12 in. loop of jejunum was found to be intensely inflamed with 'greenish black patches of gangrene scattered over its surface'. The mesenteric vessels were found to be pulsating and resection was performed. He noted that when the resected specimen was opened the mucosal gangrene was seen to extend further than was apparent from the external appearance. Histological examination of the resected jejunum showed an acute inflammatory necrosis of the mucosa. Gram staining revealed large numbers of Gram-positive bacilli in the necrotic mucosa and a culture of the bowel produced a *Clostridium welchii*. This patient did not have diarrhoea and there was no ulceration of the mucosa. Owing to the kindness of Mr York Mason we were able to obtain material from this case and Fig 11 is a Gram stain of the jejunum.

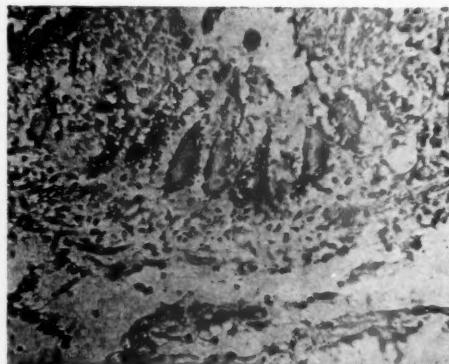


Fig 11 Necrotizing jejunitis. Gram stain showing Gram-positive rod-shaped organisms within the deeper crypts of mucosa. Culture grew *Clostridium welchii*

There is a striking similarity of clinical presentation and histological appearance between this case and our own.

We subjected the only tissue available (from Case 6) to anaerobic culture. This tissue had been preserved in formal saline for six months, but from it was obtained a pure culture of *Clostridium welchii* Type A. This was a possibility because spore formation might protect the organisms from the effects of the formalin, but it is dangerous to draw firm conclusions from this isolated finding in rather exceptional circumstances.

Treatment

As the cause of the disease is unproven, treatment is somewhat empirical but our experience suggests certain principles. These patients are shocked and should have blood replacement before surgery. At operation, resection of the diseased bowel should be wide as the mucosal gangrene is more extensive than might be expected from the serosal appearance. A proximal and distal colostomy appears to be the safest treatment as leakage occurred from all primary anastomoses in our small series. It would seem reasonable in view of the possible infective nature to administer broad-spectrum antibiotics and anti-gas-gangrene serum.

We have called this disease process necrotizing colitis because it emphasizes the two features of the pathology of the bowel wall - the necrosis of the mucous membrane and the intense inflammatory process in the mucosa. We suggest that the evidence strongly favours an infective cause even though we have not isolated the organism in culture. This hypothesis will be proved or disproved if future cases are recognized and immediate aerobic and anaerobic cultures are taken from the wall of the bowel and its lumen.

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Mr Peter F Jones (Aberdeen) showed a film illustrating A New Device to Assist in the Anastomosis Following Anterior Resection of the Rectum.

Books recently presented and placed in the Society's library

Alexander G L & Norman R M

The Sturge-Weber syndrome

pp 95 32s 6d

Bristol: Wright 1960

Braunsteiner H ed

Physiologie und Physiopathologie der weissen Blutzellen

pp 346 DM 59

Stuttgart: Thieme 1959

Bertram F J E & Michael G eds

Internationale Biguanid-Symposium am 12. und 13. Mai 1960 in Aachen

pp 167 DM 16.80

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Buxton P A

Researches in Polynesia and Melanesia

2 vols: parts 1-7

London: London School of Hygiene and Tropical Medicine 1927-1928

Brodhagen H

Local freezing of the skin by carbon dioxide snow: an experimental investigation of tissue temperature movements in depth
pp 150

Stockholm: Munksgaard 1961

Chest and Heart Association

Cardiac problems. Papers read at three symposia Revised ed pp 144 18s 6d

London: Chest and Heart Association 1961

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Pneumoconiosis - modern trends. Report of meetings held in Birmingham (April 1959) and in Glasgow (January 1960)
pp 144 18s 6d

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The transactions of the second conference on the health of executives, held in the Royal Festival Hall, London, November 24 1960
pp 112 15s

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Précis de stomatologie

3rd ed pp 957

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pp 328 DM 30.70

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Jacob de Castro Sarmento. Notas relativas à sua vida e à sua obra

pp 119

Lisboa: Edições Atica 1946

Emmrich R & Perlick E eds

Gefässwand und Blutplasma. Symposium an der Medizinischen Klinik der Medizinischen Akademie Magdeburg am 2. und 3. Oktober 1959
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Medicine makers of Kalamazoo
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La physiologie des sinus: ses applications cliniques et thérapeutiques

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Intravascular phenomena. Proceedings of the VII Conference on microcirculatory physiology and pathology, National Institutes of Health, Bethesda, Maryland, May 4 and 5 1959
Assisted by George P Fulton

pp 117 1960

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Das Praxislaboratorium; kurze Zusammenstellung der heutigen Laboratoriumsdiagnostik in der Praxis
pp 102

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Greiner G-F, Klotz G & Gaillard J

Le traitement de la paralysie faciale après fracture du rocher: techniques chirurgicales; mécanisme de la récupération
pp 181 NF 25

Paris: Arnette 1960

Grober J ed

Klinisches Lehrbuch der physikalischen Therapie
pp xi+442 DM 37.75

Jena: Fischer 1960

Grosse H

Krebssyntropien; Wahlverwandtschaften und Lokalisationsgesetze des Krebses
pp 127 DM 12.25

Jena: Fischer 1960

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Differentialdiagnose innerer Krankheiten: eine kurzgefasste Darstellung für Ärzte und Studierende
4th ed pp 678 DM 68.60

Stuttgart: Thieme 1956

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Die Pocken; Erreger, Epidemiologie und klinisches Bild. Unter Mitarbeit von A Mayr.
pp 295

Stuttgart: Thieme 1960

(Continued on p 778)

Section of Paediatrics

President B E Schlesinger OBE FRCP

Meeting February 24 1961

Some Aspects of the Management of Premature Babies [Abridged]

Dr V Mary Crosse and Dr Gerald Corney (Birmingham)

The Use of Adrenocorticotrophic Hormone in Neonatal Jaundice in Premature Babies

Early in 1959 Miss D L Ward, Sister in charge of the premature baby unit at Marston Green Maternity Hospital, Birmingham, was given six months leave of absence to take charge of the Premature Baby Unit in the Institute of Child Health, Ankara, Turkey. After being there a few months, she informed us that very few of their premature babies required transfusion for jaundice and asked if it could be due to the immediate administration of adrenocorticotrophic hormone (ACTH) to all babies developing jaundice.

Corticoids have been used in haemolytic disease, alone or with exchange transfusion, with varying degrees of success (Mayer *et al.* 1958). However, as corticoids were at that time believed to require glucuronic conjugation before elimination, it appeared that this treatment might have some risk in premature babies. It is now known that hydrocortisone is excreted mainly as free 6- β -hydroxy-hydrocortisone (Colle *et al.* 1959) and is thus not in competition with bilirubin for glucuronic acid.

Eventually ACTH was used, with careful supervision, in a few cases in the Marston Green premature baby unit. No ill-effects were apparent and the control of the jaundice was dramatic.

In August 1959 Murano suggested that corticoids activated the enzyme necessary for conjugation of bilirubin. His paper, and the impressive results being obtained in our own cases, led to the routine administration of ACTH in 1960 to all babies with a serum bilirubin level of 5 mg% or more, or reaching number 2 on Gossett's icterometer (Gossett 1960), in the Marston Green unit. The dosage of ACTH has been: 10 units b.d. for three days (or longer if the jaundice is not fading), 5 units b.d. for one day, 2.5 units b.d. for one day, 2.5 units once for one day. During the administra-

tion of ACTH, penicillin (125,000 i.u., twelve-hourly) and streptomycin (20 mg/lb/day in divided doses twelve-hourly) were given.

Table 1 compares two years, 1958 (no ACTH given) and 1960 (routine ACTH to jaundiced babies). The proportion of babies surviving the first week of life (and therefore 'at risk') was very similar in the two years. A slightly larger proportion of the babies were noted to be jaundiced during 1960, but fewer reached transfusion levels (serum bilirubin 20 mg%). During 1958, 17.3% of the survivors required transfusion, compared to only 3.6% during 1960.

Table 1
Jaundice and ACTH (Marston Green Premature Baby Unit, 1958 and 1960)

Birth weight (g)	1958		1960	
	Admissions	Alive at 1 week	Admissions	Alive at 1 week
Up to 1,500	41	9	34	13
1,501-2,000	59	54	119	105
2,001-2,500	96	93	175	162
Totals	196	156	328	280
Admissions	196		328	
Survivors	156		280	
● Jaundiced babies	63		136 (99 treated)	
● Transfused babies	27	= 17.3% of survivors	10 (1 died)	= 3.6% of survivors
Number of infections	23	= 14.7% of survivors	54	= 19.3% of survivors
Cases of kernicterus	None		None	

● Excluding Rhesus immunization.

Table 2 shows that ACTH was most effective when given early, i.e. from the day of onset of definite jaundice and before the serum bilirubin level reached 10 mg% or number 3 on Gossett's icterometer.

At Sorrento Maternity Hospital, Birmingham, ACTH was used as a routine treatment of jaundice (same indications as before) from June 11 until November 16, 1960, when a baby on ACTH

Table 2

ACTH and Jaundice (Marston Green Premature Baby Unit, 1960)
Need for replacement transfusion related to time of
administering ACTH

(a) In relation to day of onset of jaundice					
	From day of onset of jaundice	From day following	No ACTH (Jaundice less than No. 2)	Totals	
Birth weight (g)					
Up to 1,500	2	4	3	2	11
1,501–2,000	19	17 (1)	11 (3)	12	59 (4)
2,001–2,500	16	16 (1)	11 (5)	23	66 (6)
Totals	37	37 (2)	25 (8)	37	136 (10)
Average duration of jaundice (days)	5.6	6.7	7.6	7.7	6.9
(b) In relation to degree of jaundice					
	More than 5–10 mg % (No. 2–No. 3)	10 mg % (No. 3)	No ACTH (less than No. 2)	Totals	
Birth weight (g)					
Up to 1,500	8	1	2	11	
1,501–2,000	40 (2)	7 (2)	12	59 (4)	
2,001–2,500	35 (1)	8 (5)	23	66 (6)	
Totals	83 (3)	16 (7)	37	136 (10)	

Note: Numbers in brackets denote number of babies requiring replacement transfusion.

died of septicæmia (*Ps. pyocynnea*). The administration of ACTH was then suspended and it has not yet been resumed.

Table 3 compares three periods: A, January 1 to June 11, 1960 (no ACTH); B, June 11 to November 16, 1960 (routine ACTH); C, November 16, 1960 to February 17, 1961 (no ACTH). During period B, when ACTH was being used, only 4.8% of the survivors required transfusion compared with 18.4% and 18.2% during periods A and C, when no ACTH was being given.

During period B the serum bilirubin level of one baby being treated with ACTH reached 22

Table 3
Jaundice and ACTH (Sorrento Premature Baby Unit)

	Period A	Period B	Period C
	Jan. 1–June 11 1960	June 11–Nov. 16 1960	Nov. 16 1960–Feb. 17 1961
Treatment	No ACTH	Early ACTH	No ACTH
Admissions	156	127	90
Survivors (7 days)	114	104	66
Jaundiced babies	65	67	49
Transfused babies	21=18.4% of survivors	4	12=18.2% of survivors
Kernicterus	—	1 (●)	

● Serum bilirubin more than 22 mg % but too ill to transfuse (died).

Birth weight (g) of survivors	Period A	Period B	Period C
Up to 1,500	13	12 (1)	6
1,501–2,000	49 (12)	49 (3)	36 (9)
2,001–2,500	52 (9)	43 (1)	24 (3)
Total survivors	114 (21)	104 (5)	66 (12)

Note: Numbers in brackets denote number of babies requiring replacement transfusion

mg %, but he was not transfused because he was too ill with paralytic ileus. He died (in another hospital) and kernicterus was found. This patient would normally have been transfused and is therefore counted as a transfusion.

These preliminary observations all seem to indicate the usefulness of ACTH in holding the serum bilirubin levels and so reducing the need for transfusion, with its risks. On the other hand jaundice is known to occur in waves and a blind trial is now necessary to prove that ACTH was the factor concerned.

During the periods discussed the only change in treatment was at Marston Green. Halfway through 1960 (ACTH given throughout the year), a dose of 0.5 mg vitamin K₁ was substituted for a similar dose of Synkavit at birth (or on admission), but the incidence of hyperbilirubinaemia and transfusion was exactly the same in the two halves of the year.

One child in the Sorrento unit died of septicaemia while on ACTH but otherwise, in both hospitals, the incidence of infection has been approximately the same during all trial periods, both with and without ACTH.

Babies on ACTH seemed to take their feeds better, but were given only the usual amount of fluid. These babies tended to have more oedema and lose less weight during the first few days of life, but after the ACTH had been stopped they lost weight and the end-result was about the same as in babies not treated with ACTH. Serum electrolytes were investigated in a few cases and were normal. Contrary to the experience of Murano (1959), no direct-reacting bilirubin was found in the serum of infants being treated with ACTH. It will be necessary to follow-up the babies for at least one year to exclude mild degrees of kernicterus. In our experience, however, babies with kernicterus always show some signs of this complication before they leave the hospital, and none of the babies treated with ACTH (except the one with paralytic ileus and a serum bilirubin of 22 mg %) showed any signs of kernicterus.

Although Murano & Auricchio (1959) were enthusiastic about the use of prednisolone and ACTH in neonatal jaundice, Dieckhoff *et al.* (1960) reported disappointing results with 1.0–2.5 mg/kg/day of prednisolone; however, this was a small dose.

It is possible that the action of ACTH in jaundice is enzymal. A recent paper by Lanman (1961) draws attention to the enlarged fetal adrenal and its rapid involution after birth; and this could be of great importance in a baby born prematurely.

This is only a preliminary communication. A blind trial (treating comparable babies alternately with and without ACTH) is now in pro-

gress, and a further report will be given in the near future.

We are very grateful to Dr Elizabeth Lohar for analysing the figures for the Marston Green Unit; to all previous residents who have supervised the babies and done the transfusions; to the laboratory staffs of Sorrento Maternity Hospital and Marston Green Maternity Hospital; to Dr W Weiner and the staff of the Blood Transfusion Service; and to the Sisters and nursing staff of the premature baby units, for their help.

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Dr J R Hill (London)

Responses of the Newborn Mammal to Variations in Environmental Temperature and to Hypoxia

[Summary]

Recent studies have shown that the newly born mammal may differ strikingly from the adult in having a lower 'basal' metabolic rate than it should have for its size, and in having – per unit surface area – a considerably lower maximal metabolic heat production in a cold environment. In addition, the coat (or other covering) of the newborn mammal often has a lower insulating power than that of the adult. These facts underlie and contribute to, the thermal instability and low body temperature frequently shown by newly born mammals (including the human premature infant). Furthermore, hypoxia can also cause a lowering of the body temperature. These studies are described in greater detail in the references given below.

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Dr Bernard M Laurance (Derby)

The Natural History of the Premature Baby's Body Temperature

It is generally accepted that the body temperature of the full-term baby is almost identical with that of the adult, whereas the premature baby's temperature is lower; and also that it is probably unnecessary to raise the premature baby's rectal temperature above 96° F (35.5° C) and a temperature of 93° F or less has been regarded as

tolerable; as the baby matures the temperature gradually reaches adult levels (Smith 1959).

Recently there has been renewed interest in the best temperature for premature babies. In 1954 Professor Kenneth Cross suggested that instead of an environmental temperature of 90–95° F one of about 84° F might be the physiological ideal, and that the resulting lower body temperature might not be detrimental to the health of the premature babies. Over the past four years babies admitted to the Nightingale Premature Baby Unit in Derby have been nursed at these relatively low environmental temperatures.

From preliminary observations it appeared that the premature baby adopts a lower body temperature than the mature baby when nursed in an ambient temperature of about 84° F (28.8° C). Efforts were made to verify this observation.

Methods

At first the small babies were nursed in an incubator and later in Sorrento cots, sometimes covered with a Perspex top, in a warm room. In all cases ambient or environmental temperatures were recorded with the thermometer beside the baby. It should be noted that this thermometer often records 2° F (1.1° C) lower than the one at the top of the incubator.

The baby's temperature was recorded by a thermometer inserted 1 in. (2.5 cm) into the rectum for two minutes. It was taken after two minutes in the axilla during the last year of this four-year trial as we were able to confirm the work of Dr W A Silverman, of New York, that this accurately followed the rectal temperature. All temperatures were recorded three-hourly for the first forty-eight hours and sometimes for longer; thereafter they were recorded twice daily. The babies were nursed naked until their temperatures had stabilized at 95–96° F. We aimed to keep these babies in an average environmental temperature of 84° F (28.8° C), the range being 82–86° F (27.7–30° C), unless clinically there was any reason for altering this. Nevertheless, maintaining a constant temperature, even with an incubator, was difficult, and occasionally the temperature fluctuated between 80° and 90° F (26.6 and 32.2° C).

Results

Fig 1 demonstrates how the premature baby's temperature rises with increasing maturity when the ambient temperature is 82–86° F.

It shows the average body temperature at 1, 7, 14, 21 and 28 days of life in 385 babies (born between January 1957 and May 1960 inclusive) in maturity groups from 30–38 weeks. The maturity was estimated according to the mother's dates – not a reliable method, but the best available. The less mature the baby, the lower the

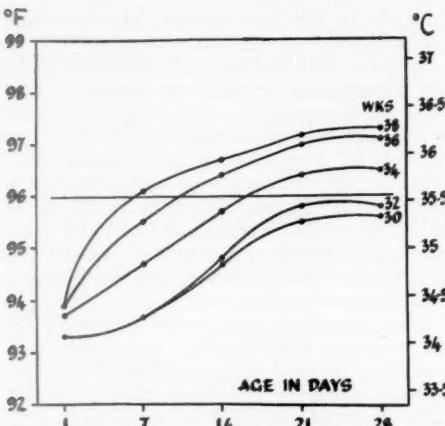


Fig 1 Temperature according to age at different levels of maturity, January 1957 to May 1960. Ambient temperature 82–86°F (27.7–30°C)

rectal temperature. The range of temperatures on Day 1 was small by comparison with those on Day 7 and partly conceals the great variability of the temperature in the first 48 hours of life and completely obscures the fall of body temperature, often considerable, that occurs within minutes of birth; it may rise again in the subsequent twelve hours or less. However, it demonstrates that the temperatures have settled to a steadier level by about the 7th day when they appear to be a truer indication of the basic temperatures of the babies at each level of maturity. The rectal temperature of the babies born before 32 weeks' gestation still have not quite reached 96°F by the time they are 4 weeks old. However, babies born after 32 weeks' gestation reach this temperature of 96°F when they are only 2 or 3 weeks old. We may expect them that a baby born at, say, 30 weeks will take longer than one born at 35 weeks to reach a temperature of about 96°F and this is demonstrated in Fig 2.

The black dots are plotted at the average temperature on the 7th day of life for each week of estimated maturity. The temperatures on the 7th day of life have been chosen because most babies' body temperatures have usually stabilized by then. Not infrequently they have stabilized by as early as the 4th day. The perpendicular lines indicate twice the standard error of the average at each week and so demonstrate the trustworthiness of the averages. The continuous line is a hypothetical one but indicates that in these conditions of nursing there is a rise of the average temperature with maturity although the range of temperature in each group is extremely variable. I am unable to explain the higher average temperatures at 28 and 29 weeks. Thus it does seem that when the

ambient temperature is 82–86°F the temperature of the baby rises in a steady gradient with increasing maturity and that the point on this gradient at which a baby's temperature settles in the first few days of life may be some guide to its maturity.

This point is illustrated by a baby who, although small, behaved like a larger one. This baby was only 1,644 g (3lb 10 oz) at birth, but was 38 weeks mature according to his mother's dates. The behaviour of his temperature seemed to confirm his maturity, for it rose and remained above 96°F within as little as 9 days of birth despite a constant but fairly low environmental temperature of between 76°F and 80°F (24.5°C and 26.6°C).

If body temperature is related to maturity it should show a correlation with birth-weight also. Fig 3 shows the average rise of premature babies' body temperatures with age in the different weight groups. Babies over 2,268 g (5 lb) are excluded, but those between 2,012 and 2,240 g (4 lb 7 oz and 4 lb 15 oz) are included for comparison with the lower weight groups. It refers to the same 385 babies as Figs 1 and 2.

At 7 days, the temperature range in each of the three weight groups is indicated. Only rarely does the body temperature fall below 90°F and when it does the babies are usually ill. They are lethargic, may suck poorly or tolerate tube feeds badly, and tend to vomit, but occasionally body temperatures have fallen as low as 87°F without apparent upset to the baby.

The temperatures of the babies in the lowest weight group take longer to rise above 96°F than those in the higher weight groups. However, the babies over 1,500 g (3 lb 5 oz) have slightly lower temperatures at first, but seem to follow the same trend after the 14th day of life as the babies over 2,000 g (4 lb 6 oz). So it appears that under these conditions the basic body temperature rises with increasing age and weight when the environmental temperature is kept as constant as possible between 82°F and 86°F. There is no sex difference in this rise.

The mortality rate for these 385 babies (seen between January 1957 and May 1960) was approximately 26%. This rate is comparable with the results from other centres in England where babies have to be transported some distance from outside hospitals or homes.

In June 1960, as the result of discussions with Professor Kenneth Cross, the ambient temperature of the premature babies admitted to our unit was raised from 84°F to between 88°F and 90°F (31.1°C and 32.2°C). Otherwise conditions remained exactly the same as before.

There was still a similar rise of body temperature on the seventh day with increasing maturity (Fig 4) but all the temperatures were at a higher level (upper line) than in those nursed at the lower

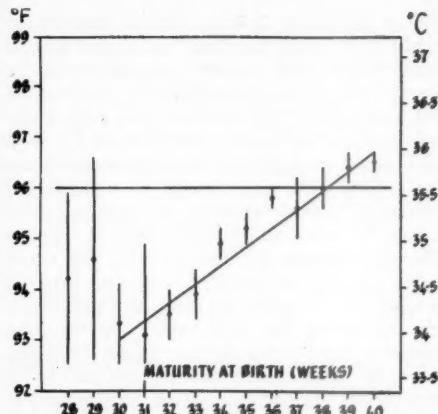


Fig 2 Average temperatures on the seventh day of life according to maturity at birth (limits are at ± 2 standard errors), January 1957 to May 1960. Ambient temperature 82-86°F.

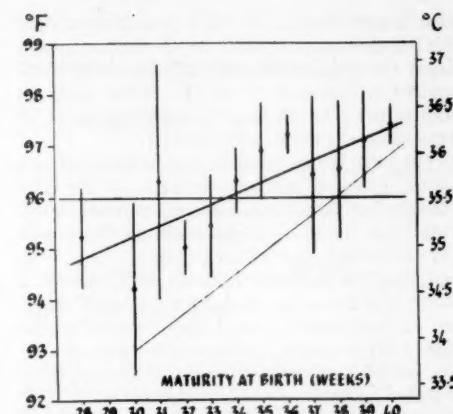


Fig 4 Average temperatures on the seventh day of life according to maturity at birth (limits are at ± 2 standard errors), June to December 1960. Ambient temperature 88-90°F.

ambient temperature (lower line transposed from Fig 2). The same was true of the temperatures at 1, 7, 14, 21 and 28 days of life at maturity levels of 30 to 38 weeks.

When they are compared with different weight groups (Fig 5) it is significant that the average temperatures of the babies in the lowest weight group below 1,500 g reached nearly 96°F as early as the 7th day of life, whereas those in an ambient temperature of 84°F took four weeks to reach the same temperature. The mortality for this group was 25% – almost the same as the previous group.

Conclusions

(1) The natural fall in body temperature immedi-

ately after birth and the subsequent rise within twelve hours may not always be appreciated. Consequently the medical attendant may try to warm the baby too quickly, especially if the temperature taken, say, half an hour after the birth is found to be 93°F or lower. This fall and subsequent rise is probably related to maturity and birth weight, but other factors including the temperature of the room may be important.

(2) The basic temperature may be defined as the lowest rectal temperature reached between the fourth and seventh day of life when the baby has been nursed in a temperature between 80° and 90°F. On average, the lower the birth weight and the less mature the baby, the lower will be its

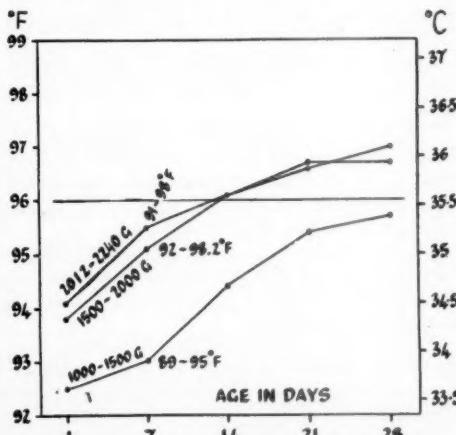


Fig 3 Average temperature according to weight, January 1957 to May 1960. Ambient temperature 82-86°F.

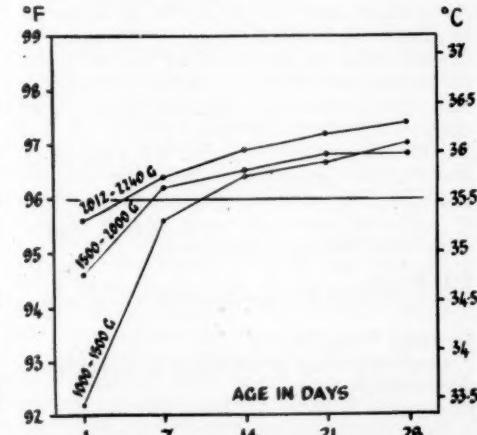


Fig 5 Average temperature according to weight, June to December 1960. Ambient temperature 88-90°F.

basic temperature. This basic temperature rises with increasing age to reach 96° F within approximately two weeks of estimated full maturity if the ambient temperature is 84° F. If the ambient temperature is 88° F, then the baby reaches 96° F about six weeks before full maturity.

(3) The basic temperature cannot be accepted as a reliable index of maturity because of the considerable individual variation; nevertheless it has often been found to confirm the mother's own estimate of the length of her gestation.

(4) I think it probable that an environment of 88–90° F is better for the baby than one of 84° F but the best environmental temperature for premature babies is still to be determined and we need to know whether this should aim at keeping them at their 'neutral' or 'critical' temperature. This paper suggests only that it may not be necessary to keep the body temperature of premature babies as high as full-term ones. Indeed such attempts may result in undesirable hyperthermia although I know of no proof that this is so.

It is difficult to decide whether the lower environmental temperatures have had an adverse influence on these babies. Generally they thrive satisfactorily as long as their rectal temperatures do not fall below 90° F. I have the impression that jaundice is less common in the babies nursed at the lower environmental temperature. I am not maintaining that a low environmental temperature is the only way in which premature babies can be brought safely to maturity, but when I started this trial it seemed likely that such a temperature could conceivably decrease the demands made upon the babies' immature metabolism. For the nurse these low temperatures would obviously be welcome.

Acknowledgments: I would like to thank successive registrars, Drs A Ferguson, D Plowman and B Hutchinson Smith, and Sister McDevitt and her nursing staff for their continued, enthusiastic help with this work. Mrs A Ridgard, comptometer operator with the Derby Group of Hospitals, and Drs G H Jowitt, H Ruben and D F Kerridge of Sheffield University kindly helped me with the statistics. Lastly, I record my thanks to Professor D V Hubble, who made many valuable suggestions when I first started this work.

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Dr Hugh Jolly (London)

A Controlled Study of the Effect of Temperature on Premature Babies
[Summary]

Details were given of a controlled study planned to compare the survival rate and clinical behav-

iour of premature babies, half of whom were nursed in a warm and half in a cool atmosphere. Only babies requiring incubator nursing were included. It was found that 9·5% more of the cold babies died. This was not quite statistically significant but the results were sufficient for us to feel that we should nurse our babies warm and that it would be unjustifiable to continue the experiment in order to try to get statistical satisfaction. We were also impressed by the clinical difference between the two groups. The warm babies appeared more comfortable than the cold ones, whom the nurses described as being miserable and feeling like 'cold apples'. At the same time we regard it a mistake to overheat the babies and if their temperature rose to more than 98° F the large ones in particular often became restless and perspired. From these results a rectal temperature of 97–98° F appears to be the ideal.

(This paper will be published in full elsewhere.)

Meeting March 24 1961
*at the Queen Elizabeth Hospital for Children,
Hackney Road, London*

Cases of interest and demonstrations illustrating the current work of the hospital were shown as follows:

In the section on respiratory conditions, aspects of the management of pulmonary complications of cystic fibrosis of the pancreas, were shown, together with a demonstration of the X-ray changes in staphylococcal pneumonia.

Gastroenterology was represented by studies of surgical treatment of some congenital bowel abnormalities, the work of the Gastroenteritis Unit, and malabsorption syndromes.

There were demonstrations of vesico-ureteric reflux and ileal-loop diversion of the urinary tract.

The results of plastic surgery in ectopia vesicæ, facial deformity and severe burns, together with aspects of general medical and anaesthetic management in this specialty were shown alongside several unusual skin conditions.

Patency of the ductus arteriosus in premature babies associated with respiratory difficulties was demonstrated, together with interesting cases of congenital heart disease.

Studies of hypothyroidism, salt-losing syndrome of infancy, prenatal exogenous virilization, and chromosomes in the webbing syndrome were shown.

The importance of early recognition of metabolic disorders of infancy was demonstrated with examples of several rare conditions.

Section of Endocrinology

President H L Sheehan MD

Combined meeting February 22 1961 with the
Society for Endocrinology

Endocrine Aspects of Pregnancy and Parturition

Adrenal Cortex and Pregnancy

by C L Cope DM (*London*)

That the adrenal cortex tends to enlarge during pregnancy has been known for a great many years. It has been known, too, since the work of Venning in 1946, that the amount of active adrenal cortical hormone in the urine is increased in late pregnancy, as judged by bioassay of urinary extracts.

This we were able to confirm some years later. It will be recalled that Hench *et al.* (1949) had attributed the clinical improvement seen in pregnant rheumatoid arthritics to an assumed increase in adrenal activity based on these and similar observations. When it was recognized that the active hormone was in fact cortisol and chemical methods of estimating this were worked out, it was found that the level of plasma cortisol rose progressively during pregnancy, reaching the highest peak at the time of labour (Bayliss *et al.* 1955).

This raised several fundamental problems: (1) Was the rise due to increased production of cortisol by the adrenal or was it due to reduced rate of destruction? (2) Was there any formation of cortisol at another site, such for instance as the placenta? (3) Why was there no clinical development of cushingoid features or other evidences of hypercorticism as a result of the raised plasma levels?

(1) It might be thought that the question of increased production could have been solved by some of the widely used indices of adrenal function—some of the urinary steroid analyses. The fact that no firm conclusion has been reached by this means, and indeed that two schools of thought persist, is surely a reflection of the unreliability of such tests for revealing moderate changes in adrenal activity.

The availability of isotope-labelled steroids has made it possible to solve this problem. By administering a dose of the isotopic cortisol, and observing the extent to which this is diluted by

admixture with the non-isotopic cortisol of endogenous origin, the daily production of cortisol by the body can be calculated. Observations in late pregnancy made in a series of cases show a mean cortisol production rate of about 25 mg daily, compared with a mean of about 11 mg daily for a group of non-pregnant women of the same age range (Cope & Black 1959). It is interesting to note how well those estimates, derived from isotopic techniques, agree with estimates derived by purely clinical observation. Patients with Addison's disease have been successfully brought to full term on doses of cortisone acetate varying from 10 to 50 mg daily. Most require about 25 mg daily and one patient who was allowed to choose her own dose developed clear signs of overdosage on 50 mg daily. Isotopic methods have also shown that the daily production of aldosterone is increased in pregnancy to about three times the non-pregnant level (Jones *et al.* 1959).

(2) Several groups have shown that injected cortisol, whether natural or isotopic, disappears at about half the normal speed in women in late pregnancy (Migeon *et al.* 1957).

(3) The lack of hyperadrenal symptoms is explained by the finding that the greater part of the circulating cortisol is bound to protein and is probably thereby temporarily inactivated. The proportion bound is greatly increased in pregnancy, and the rise in binding protein is found to be produced by oestrogens, either natural or synthetic (Mills & Bartter 1959, Taliaferro *et al.* 1956).

Maternal circulating cortisol crosses the placenta into the fetus fairly readily and the products of its metabolism equally readily pass out of the fetus into the maternal venous system. Whether the placenta itself manufactures any cortisol is as yet unknown, but if it does the amount is likely to be relatively small. Metabolites derived from cortisol are only found in the urine in trace or very small amounts when steroid therapy is withheld from a pregnant addisonian patient.

Thus in pregnancy there appears to be (a) In-

creased formation of cortisol, (b) decreased destruction, and (c) increased binding or inactivation of the circulating cortisol.

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Pregnancy and Diabetes

by Wilfrid Oakley MD FRCP (London)

In this communication I shall confine myself to a brief consideration of the main problems of diabetic pregnancy from the physician's viewpoint and leave the presentation of results to Sir John Peel. The chief problem is the foetal loss rate, maternal mortality being now almost as low as that in normal women; maternal morbidity is another matter. The suitability of any diabetic woman to embark on pregnancy may be viewed from the standpoint of heredity, maternal morbidity or in relation to the outcome of the pregnancy. The diabetic status has usually been considered chiefly in relation to the probability of the production of a live child which survives, but it is important to take into account the effects of pregnancy on the diabetic mother. In a personal series of 275 diabetic pregnancies the effect of the pregnancy was investigated in relation to: (1) subsequent insulin requirement, (2) retinopathy, (3) hypertension, and (4) albuminuria.

In a few cases the insulin requirement was greater and in a few less than before pregnancy but in the last 80 consecutive pregnancies of this series there was no significant increase in insulin requirement. In 2 patients there was severe atypical retinopathy with haemorrhages and papilloedema which cleared completely after delivery, and in 2 patients typical retinopathy progressed during and immediately after pregnancy. In 10 patients with retinopathy there was no evidence of progression. These results are too scanty to allow conclusions to be drawn, but it seems that pregnancy must be regarded as potentially dangerous in those diabetics with the vascular or pre-retinal lesions which so often give rise to vitreous haemorrhage and retinitis proliferans.

Hypertension and albuminuria were considered

in relation to toxæmia of pregnancy, of which the incidence has fallen in the past three years at King's College Hospital. In a consecutive series of 222 diabetic pregnancies, 24 were complicated by toxæmia. Three of these 24 were untraced, 1 mother died with eclamptic fits and cholæmia, and 1 had uræmia due to chronic nephritis. In 13 of the remaining 19 cases there was no evidence of change following the toxæmic pregnancy. In the other 6 cases there was a significant rise in blood pressure in 3 and albuminuria in 1; 2 developed retinopathy. As the minimum duration of the diabetes in these cases was ten years, and the interval between the toxæmic pregnancy and the follow-up examination varied from one to eight years, it is impossible to assess the significance, if any, of toxæmia of pregnancy in relation to the incidence of subsequent complications.

The effect of the diabetic status on the outcome of the pregnancy is based on a series of 733 pregnancies. The severity of the maternal diabetes does not appear to be directly related to fetal survival; the same can be said of the age at onset and the duration of the disease. In our experience foetal loss cannot be attributed to any large extent to toxæmia of pregnancy. In 1942 Lawrence and I published the results of a series of 54 diabetic pregnancies and drew attention to the striking relationship between diabetic control and foetal survival. In the light of subsequent work it appears that in the past we have been content with too low a standard of diabetic control, and re-analysis of our results on a stricter criterion has confirmed this relationship. In a series of 109 pregnancies the foetal survival rate in patients with good diabetic control was 81% and that in 101 patients delivered at King's College Hospital during the past three years was 86%; if congenital deformities incompatible with life are excluded from this last series the survival rate is 89%. The difference between these figures may well be related to the fact that, for the past three years, all pregnant diabetics have been admitted to hospital at the 32nd week.

Analysis of the 12 cases of foetal loss showed that in 6 the control of the maternal diabetes, either before or after admission, was less than good, while in the remaining 6 it was good throughout pregnancy. Assuming that control of the maternal diabetes is the sole factor in determining foetal survival 6 of the 12 foetal fatalities in this series of 101 pregnancies might be accounted for, leaving 6 or 6% attributable to some other cause. It is perhaps more than a coincidence that this figure approximates closely to that given by some authors for the foetal loss rate in pre-diabetic mothers.

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Management of the Pregnant Diabetic

by Sir John Peel KCVO FRCOG FRCS (London)

The problems relating to perinatal mortality in diabetic pregnancy alone are presented. The results of 563 pregnancies managed at King's College Hospital over a thirty-year period are analysed. The cases fall into 3 groups covering approximately one decade in each group (see Table 1).

Table 1
Maternal and fetal mortality in 563 pregnancies

	No. of cases	Maternal mortality %	Total fatal loss %
Before 1941	49	2.2	32.6
1941-1948	141	1.4	25.4
1949-1952	102	1	25.5
1953-1957	165	0	23.8
1958-1960	106	0	14.1

The cases in the last decade fall conveniently into 3 phases:

- (a) 1949-1952: During this period hormone therapy (stilboestrol and ethisterone) was employed.
- (b) 1953-1957: Admission of selected cases for intensive in-patient therapy.
- (c) 1958-1960: Admission of all cases at 30-32 weeks for intensive in-patient therapy (control of diabetes, bed rest twenty hours per day, and treatment of hypertension and/or oedema).

It is only in the last phase that the perinatal mortality has improved. Although there is still very little improvement in neonatal death-rate, stillbirths (fresh and macerated) have been reduced to 3.7% (Table 2).

Table 2
Fetal mortality in 563 pregnancies

	No. of cases	Stillbirths No.	Stillbirths %	Neonatal deaths No.	Neonatal deaths %	Total fatal loss No.	Total fatal loss %
Before 1941	49	11	22.4	5	10.2	16	32.6
1941-1948	141	16	11.2	20	14.2	36	25.4
1949-1952	102	9	8.8	17	16.7	26	25.5
1953-1957	165	24	14.2	16	9.6	40	23.8
1958-1960	106	4	3.7	11	10.4	15	14.1

Intrauterine fetal death is particularly liable to occur in the following circumstances: (1) Uncontrolled diabetes, (2) in the presence of hydramnios, (3) when the baby becomes grossly overweight, (4) in the presence of severe hypertension and/or albuminuria, and (5) in pre-diabetes.

There is an urgent need for more information about what happens during a pre-diabetic pregnancy. Analysis of 27 patients seen, in whom diabetes developed in association with a previous

pregnancy shows the following details of those pregnancies: Glycosuria, 5 cases; stillbirth (baby over 10 lb), 6 cases; live baby (over 10 lb), 5 cases; stillbirth (baby normal size), 4 cases; early neonatal death (baby normal size), 5 cases; and apparently normal pregnancy, 2 cases.

The fact that glycosuria occurred in only 5 cases shows that hyperglycaemia is unlikely to be the primary cause of the excess foetal weight in prediabetic pregnancy, and probably not in diabetic pregnancy. Hormone changes in pregnancy have been demonstrated, e.g. increased plasma cortisol, increased urinary aldosterone, and increased blood progesterone. Glucose tolerance is known to be affected in pregnancy (diabetogenic effect of pregnancy). In some prediabetic pregnancies the patient becomes diabetic (hyperglycaemia - abnormal glucose tolerance curve), but in many no glycosuria occurs. Information concerning glucose tolerance and blood sugar levels in pre-diabetic pregnancy is for obvious reasons very scanty, but is urgently required. Careful post-mortem studies on stillborn babies or babies dying in the early neonatal period, in suspected pre-diabetic pregnancy are also urgently required, with particular emphasis upon the amount of islet tissue in the fetal pancreas. There is a definite relationship between foetal weight and the amount of islet hyperplasia.

Experimental work at King's College Hospital during the last few years has failed to show any evidence of placental insufficiency in diabetic pregnancies in which intrauterine foetal death had occurred. Determinations of uterine blood flow, the oxygen saturation of foetal cord blood and fetal haemoglobin levels have been carried out.

A further effect of the recent regime of hospitalization and rigid control of the diabetic condition has been a decrease in foetal and placental birthweights. This is not due simply to a decrease in fluid retention. The incidence of severe hydramnios has also decreased, and there has been a reduction in the average amount of liquor. Pre-eclamptic toxæmia has only occurred in 8% of patients, in 5 of whom there was a previous chronic hypertension. All the cases were very mild.

The aim of obstetric management has been to allow the pregnancy (in the absence of complications) to continue into the 38th week. This is later than was our previous practice. Each case must be considered individually. Routine termination at a particular date arrived at arbitrarily does not give the best foetal outcome. Previous obstetric history, present state of the diabetic condition and an exact obstetric assessment are necessary before the appropriate date for termination of the pregnancy, either by Cæsarean section or induction of labour, can be decided.

The Surgery of the Thyroid in Pregnancy

by M J Lange FRCSED (London)

At the Endocrine Unit, New End Hospital, we do not usually regard pregnancy as a contraindication to thyroidectomy. If surgery is decided on, we prefer to operate between the third and sixth months of pregnancy. These patients conveniently fall into two categories: those with non-toxic goitres, and those with thyrotoxicosis.

Non-toxic Goitres

Those patients with small symptomless lobulated goitres, usually a persistent puberty type of goitre, need no treatment. A little increase in size during pregnancy is not unusual, and it is as well to inform the patient of this. If it is a nodular goitre, small and symptomless, and there is no undue increase in size reported, surveillance only is recommended.

If there are pressure symptoms — tightness in the throat, feelings of constriction in the neck, dry irritable cough, dysphagia, stridor, &c. — thyroidectomy is advised. Large nodular goitres, even though apparently symptomless, are usually referred for surgery as a prophylactic measure.

Non-pregnant patients presenting with a discrete nodule in the thyroid are subjected to radio-iodine studies to determine the functional capacity of the nodule. The functionless 'cold' nodule is immediately referred for surgery in view of the high incidence of neoplastic change. However, in the pregnant patient radioactive iodine investigation is contraindicated and it is wisest to recommend surgery in all these cases.

If the goitre has recently increased in size, if there is accompanying local discomfort, voice changes, a suspicious hardness, or if enlarged regional lymph nodes are present, then prompt exploration of the goitre, irrespective of the stage of pregnancy, is indicated. Though no case of malignant goitre was encountered in our series, it is considered that neoplastic changes occurring during pregnancy would be of the more rapidly growing type.

Thyrotoxicosis

In the presence of florid thyrotoxicosis, irrespective of the stage of pregnancy, the cardinal principle is to control the thyrotoxicosis as soon as possible by means of antithyroid drugs. By preference we use carbimazole in a dosage of 10 mg, thrice daily. If there are side-effects to this drug we employ potassium perchlorate. As soon as the thyrotoxicosis comes under control, we decide on definitive treatment. Thus, if the thyrotoxicosis is controlled by the 6th month,

Lugol's iodine is added to the carbimazole and two to three weeks later the patient is admitted for thyroidectomy. But if the toxicity is not controlled by the 6th month, surgery is postponed and the antithyroid drug (in increased dosage if necessary) is continued until the toxicity is brought under control and then the dose is gradually reduced. Reduction is continued until a dose is arrived at which is large enough to control the thyrotoxicosis, yet not to induce hypothyroidism. The daily dose of carbimazole may be as low as 2.5 mg or as high as 20 mg.

This regime requires the most meticulous supervision — too rapid a reduction in the dosage may result in relapse of the thyrotoxicosis, whilst persevering with the full dose, in spite of toxicity coming under control, will almost certainly result in hypothyroidism. In this event, the foetus may develop, and be born with, a goitre.

When the patient is balanced on a maintenance dose, it is continued throughout the remainder of pregnancy. After parturition the whole question can be reviewed. As a rule these patients come to surgery. It is not unusual for a proportion of them to go into remission as term approaches, so that the antithyroid drug may be stopped for the remainder of the pregnancy.

To bring the thyrotoxic patient under control usually takes six to twelve weeks' treatment with antithyroid drugs. It follows therefore that the pregnant thyrotoxic seen before the 4th or 5th month of pregnancy will usually be treated by detoxication and surgery, whilst those seen for the first time at the 5th or 6th month, will be treated by antithyroid drugs, at first in therapeutic and subsequently in maintenance doses.

In cases of *mild thyrotoxicosis*, the exhibition of antithyroid drugs is not as a rule necessary, Lugol's iodine for the two to three weeks immediately before surgery being sufficient. These patients, if seen in the last few months of pregnancy, are best treated with antithyroid drugs throughout the remainder of gestation.

The occasional pregnant thyrotoxic, in the younger age group with the more stable temperament and with a small lobulated goitre that responds quickly to anti-thyroid drugs, may be worthy of trial treatment by medical means. This type of patient will occasionally remit on prolonged antithyroid drug treatment.

No special precautions are needed for these cases undergoing operation. They are admitted one or two days before operation. Anaesthesia is induced with Pentothal and maintained with nitrous oxide and oxygen, and perhaps halothane, the anaesthetist taking steps to avoid the patient straining and reducing post-operative nausea and vomiting to a minimum. We are perhaps a little

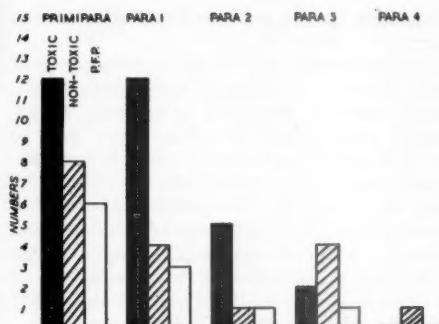


Fig 1 PFP=pregnancy as a precipitating factor

more liberal with postoperative sedatives in these patients. Like the non-pregnant patient, these cases are up on the day after operation and are usually discharged 8 to 10 days after operation.

Review

In a recent series of 3,500 consecutive thyroidectomies performed between 1947 and 1959 there were 49 pregnant patients. All were between the ages of 20 and 45, the majority under 30. In most patients at the time of operation, the pregnancy had advanced to between the 12th and 24th weeks. Three were just beyond, and two just under this period. Twenty of the 49 were primi-

paræ, and together with the para-I patients accounted for nearly 75%. The non-toxic, the mildly toxic and obviously toxic each accounted for approximately one-third of the total.

In certain instances, taking into consideration the history, the patient's domestic background and psychological make-up, we concluded that the pregnancy itself might have precipitated the thyrotoxicosis. It was thought that this had occurred in 11 of the 31 toxic patients (Fig 1). The primiparæ and the para-I patients account for 77% of the toxic cases. Pregnancy as a precipitating factor was not unexpectedly most evident in the primiparæ.

Follow up: Of the 49 patients, 44 were seen one month after discharge from hospital and found to be fit and well with the pregnancy proceeding normally. Trace has been lost of 4. A further 8 were lost trace of subsequently and the result of parturition in these is not known.

In this series there occurred only one known abortion following the operation.

Conclusion. There appears to be no increased hazard to the pregnant patient undergoing thyroidectomy, provided the thyrotoxicosis has been controlled and operation is undertaken between the 12th and 24th weeks.

(For list of other papers read see p 754)

Meeting April 26 1961

Short Papers

Hyperinsulinism in the Pathogenesis of Neuroglycopenic Syndromes

by Vincent Marks BM MRCPED, David Marrack MD and F Clifford Rose MB MRCP (London)

Harris (1924) introduced the term hyperinsulinism to describe the condition in which symptoms appeared spontaneously similar to those produced by the administration of excess insulin. Gorsuch & Rynearson (1944) suggested that hyperinsulinism should be reserved to describe the entity of insulin overproduction by an islet cell tumour (insulinoma) and it is in this sense that it will be used in the present communication.

Hyperinsulinism is an important cause of neurological disease. Though generally considered to be rare this rarity may be more apparent than real. This report is based upon 16 cases, of which 9 were first recognized within the past two and a half years. Of these 9 patients an islet cell tumour was removed with benefit in 8; the ninth patient

refused operation though the diagnosis was not in doubt clinically. One additional patient with symptoms and occasional low blood sugars was operated upon but no tumour was found.

The tumour was examined histologically in 13. It was benign in 7, recurrent and multiple in 1, metastatic in 4 and probably malignant in another. Three patients refused operation. One patient with a proven tumour had renal glycosuria and amino-aciduria.

A delay in diagnosis may have far-reaching and disastrous consequences. One young woman of 23, seen ten years ago, died within a year of the onset of symptoms. The true nature of her illness was not suspected until a small, benign β -cell adenoma of the pancreas was found at autopsy.

The failure to consider the possibility of hyperinsulinism as an aetiological factor is responsible for misdiagnosis in most cases. The symptomatology is inconstant from patient to patient; and in the same patient from time to time. It

may closely resemble any one of a number of organic or functional nervous disorders.

In some patients the diagnosis is entertained but discarded too readily on the result of a glucose tolerance test or for some other inadequate reason.

The occurrence of symptoms which are relieved by glucose, in the presence of a normal or above normal blood sugar led Sigwald (1932) to describe them as glycopenic to indicate their closer dependence on tissue than on blood glucose concentration. We have extended Sigwald's concept and describe as neuroglycopenic the signs and symptoms which develop when the supply of metabolizable carbohydrate available to the neuron is inadequate. Hypoglycaemia is only one, though the best characterized, cause of neuroglycopenia, which can be produced by any abnormality that prevents carbohydrate from entering the neuron or its proper participation in metabolism. As hypoglycaemia may occur without neuroglycopenia, and neuroglycopenia without hypoglycaemia, we feel the designation of neuroglycopenic syndromes as 'hypoglycaemic' is a misnomer.

We have classified the neuroglycopenic syndromes that occur in patients with hyperinsulinism into four types: (1) Acute, (2) subacute and (3) chronic neuroglycopenia; and (4) hyperinsulin neuropathy.

(1) Acute neuroglycopenia produced by insulin overdosage has been studied intensively. There is sweating, vasodilatation, hunger, numbness or tingling of the tongue and lips, rapid heart action, double vision and unsteady gait. In more severe attacks consciousness is lost (Marble 1959). The part which adrenaline plays in the production of the symptoms of acute neuroglycopenia has been exaggerated (French & Kilpatrick 1955, Ginsburg & Paton 1956). The syndrome is uncommon in patients with hyperinsulinism though frequent in those with reactive hypoglycaemia.

(2) Although retrograde amnesia, or even unconsciousness, occurs at some time or other in almost every patient with insulinoma it is only infrequently preceded by sweating, hunger, numbness or tachycardia. With fasting there is usually a progressive loss of intellectual ability with lassitude merging into stupor and finally coma. The symptoms and changes in the electroencephalogram (EEG) associated with both acute and subacute neuroglycopenia are usually rapidly reversed by glucose. Glucocorticoids (cortisol: 100 mg intravenously) may hasten recovery when it is delayed or fails to occur despite normoglycaemia. This has been demonstrated repeatedly in patients undergoing deep insulin coma therapy (Kay 1959, personal communication) and was also observed in one of our patients with hyperinsulinism. It is postulated that cortisol makes

extracellular glucose more readily available to the neurons.

(3) Many patients with hyperinsulinism present with a variety of progressive psychiatric syndromes and are diagnosed as hysteria, schizophrenia and organic dementia. There may be few or no episodes of acute or subacute neuroglycopenia and because of this the true nature of the illness is unsuspected. Short-term treatment with carbohydrates seldom produces benefit. However, gradually, with prolonged normoglycaemia, there is intellectual improvement and, regardless of the severity of the initial neural damage, useful restoration of function may be expected.

(4) Hyperinsulin neuropathy was not observed in any of our patients. Mulder *et al.* (1956) have reviewed this condition which possibly represents only a specific example of irreversible neuronal damage from profound neuroglycopenia.

The pathogenesis of neural dysfunction in hyperinsulinism is not clear. The confused relationship of blood glucose to symptoms is partly due to the non-specificity of conventional methods for glucose estimation. We have found low blood glucose, i.e. below 40 mg/100 ml (glucose oxidase method: G.O.), on several occasions when the concentration measured by non-specific reducing methods was well within the normal range. However we have been unable to correlate closely the blood glucose concentration with the severity and nature of the symptoms. One patient, at the time he was entering an acute neuroglycopenic episode had a normal blood glucose concentration (G.O.); others have retained consciousness when the blood glucose was less than 10 mg/100 ml.

Kauvar & Goldner (1954) have discussed their hypotheses for this lack of relationship between the blood sugar and neuroglycopenia.

The amount of glucose in the blood does not necessarily reflect its utilization by the brain. The brain appears to be unique in that its glucose uptake does not depend upon the concentration in the blood (Rowe *et al.* 1959). Impaired glucose transport across the cell membrane may occur or intracellular metabolism may be deranged. This may account for the development of neuroglycopenia at higher blood sugar levels than normal in patients with cortisol deficiency (Thorn *et al.* 1940) and in persons given the glucose congener 2-deoxy-D-glucose which interferes with glucose metabolism (Laszlo *et al.* 1961).

The possibility that the rate of change, rather than the absolute level, of glucose in the blood is responsible for producing symptoms has some support. The mechanism is unknown.

It has been suggested that there is an adaptive mechanism which permits adjustment of neural metabolism to unphysiologically low blood sugar

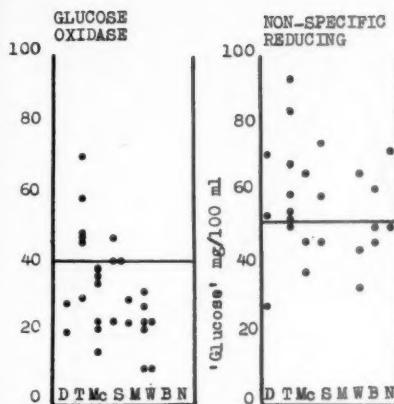


Fig 1 Concentration of glucose, measured by glucose oxidase (left) and non-specific reducing methods (right) in first blood sample withdrawn after a minimum twelve-hour fast in 8 patients with proven insulinomas. Both techniques were not used on every specimen. Horizontal lines indicate the generally accepted upper limit for hypoglycaemia by each method (40 mg/100 ml glucose oxidase; 50 mg/100 ml non-specific reducing). Twenty-one of 27 samples analysed (78%) for glucose by glucose oxidase, and 10 of 24 (42%) by non-specific reducing methods showed hypoglycaemia.

levels. Williams (1959) has stated that the normal EEG which may occur with chronic hypoglycaemia can become abnormal when normoglycaemia is restored.

The low blood sugar level may not be the sole cause of cerebral dysfunction. The nearly or completely normal EEG which may occur with hypoglycaemia alone, can be converted to an abnormal one by the simple manoeuvre of altering the blood pH by overbreathing. Reversion to normal occurs when overbreathing is discontinued or the hypoglycaemia corrected.

Fraser *et al.* (1938) suggested that insulin might be toxic, especially in the presence of a low tissue glucose concentration. Support for this comes from the observations by Heller & Hesse (1960) that the respiration of isolated sciatic nerve is depressed when insulin is given to the intact animal. It is enhanced by insulin *in vitro*. This raises the possibility that degraded or altered, but not native insulin, impairs neural function. We have observed that glucagon and tolbutamide predispose to neuroglycopenia in the presence of a low blood glucose level.

The diagnosis of hyperinsulinism requires the demonstration of fasting hypoglycaemia the various causes of which are discussed by Howard (1955) and Conn & Seltzer (1955).

Hypoglycaemia is an indication that glucose has been removed from the blood faster than it has been replenished. It has been shown that in hyperinsulinism the rate of glucose disappearance

from the blood is usually normal though sometimes it is either increased or decreased (Marrack & Marks 1961). It is suggested that in most cases hypoglycaemia from hyperinsulinism is due to the impaired release of glucose by the liver.

Oral and intravenous glucose tolerance tests designed to measure the peripheral glucose uptake are of little value in the diagnosis of hyperinsulinism, and may be frankly misleading.

Fasting hypoglycaemia is not always easily demonstrated though it is facilitated by using a glucose oxidase method for glucose analysis (Fig 1) and also by activity, which increases peripheral glucose uptake. Provocative tests are valuable aids to diagnosis; though none is specific or absolute we have found the glucagon and tolbutamide tests particularly useful and the results of these are discussed in the next paper.

Acknowledgments: We should like to thank the Physicians of the National Hospital, Queen Square, and the Atkinson Morley Hospital for permission to study patients under their care. One of us (V. M.) wishes to thank the Medical Research Council for a clinical fellowship during tenure of which part of the work was carried out.

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Glucagon and Tolbutamide Tests in the Recognition of Insulinomas

by David Marrack MD, F Clifford Rose MB MRCP and Vincent Marks BM MRCPED (London)

In the preceding paper we pointed out some of the problems of correlating the symptoms and signs of neuroglycopenia with blood glucose concentrations in patients with hyperinsulinism. These problems complicate the diagnosis of insulinoma which depends upon the recognition of hypoglycaemia.

Although fasting for up to forty-eight hours with periods of exercise reveals most cases, never-

theless a simple and reliable screening procedure is needed, which will provoke attacks at convenient times of the day in the quite numerous patients who have symptoms and signs which might be due to an insulinoma. The effects of glucagon (Marks 1960) and tolbutamide (Gittler *et al.* 1958, Fajans & Conn 1959, Fajans *et al.* 1961) on blood glucose concentration and the development of neuroglycopenia have been studied in cases of insulinoma and appear to fulfil this requirement. In our tests the blood glucose was estimated by a specific glucose oxidase method (Marks 1959).

Glucagon Test

In the first 4 patients with insulinoma, previously reported by Marks (1960), intramuscular glucagon precipitated neuroglycopenia in association with an abnormally low blood glucose concentration. This pattern of response has been seen neither in normal subjects nor in patients who were believed not to have insulinomas. It is, however, recorded in idiopathic hypoglycaemia of infancy (Kinsbourne & Woolf 1959, Cochrane *et al.* 1956).

The observations have been extended using the same method and our results in 33 control subjects and in 10 patients with insulinomas are shown in Fig 1. The two features of importance seem to be: (1) A normal rise in the blood glucose

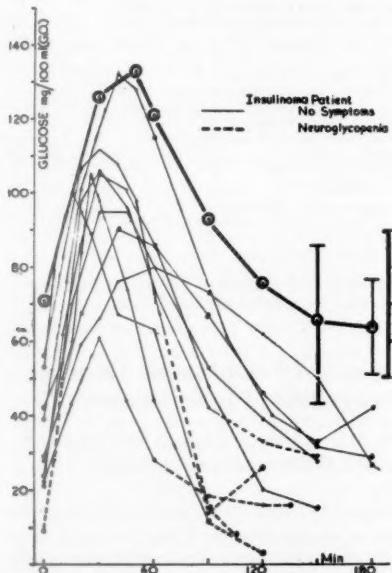


Fig 1 Blood-glucose response, in 10 patients with hyperinsulinism, to 1 mg of glucagon I.M. The mean response in 33 control subjects is shown by the heavy line. The vertical lines at 150 and 180 minutes represent $\pm 2 \times S.D.$. Normal fasting range is shown by the column on the right. Interrupted line indicates periods of neuroglycopenia

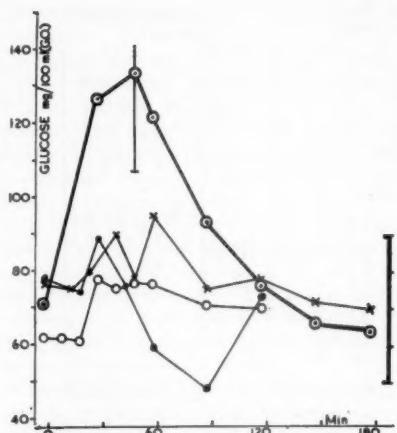


Fig 2 Blood glucose response in three patients with liver disease to 1 mg glucagon I.M. Controls as in Fig 1

concentration (not less than 40 mg%) between 15 and 30 minutes after the injection of the glucagon; and (2) A fall in blood glucose to levels less than 45 mg% at or before 180 minutes, with little, if any, rise subsequently.

Some patients with liver disease may not show the normally expected rise in blood glucose concentration and 2 such patients shown in Fig 2 had suffered spontaneous attacks of hypoglycaemia.

Six out of ten patients with insulinomas had low fasting blood glucose concentrations before starting the test but only 1 had symptoms at this time; these disappeared as the blood glucose level rose during the test and reappeared as it fell. In 3 cases the test had to be stopped because severe symptoms of neuroglycopenia developed. The mean rise in blood glucose in the 10 patients was similar to that in the control group. In contrast to the control group all the patients with insulinoma developed hypoglycaemia within one and a half to three hours after the injection of glucagon, though neuroglycopenia was not always apparent.

Two patients with reactive hypoglycaemia were studied and the response was normal, confirming the findings of Alivisatos & McCullagh (1955). This test seems to us to be valuable in screening patients for insulinomas as well as in differentiating the causes of spontaneous hypoglycaemia.

It is of interest that the hypoglycaemia induced by this test in patients with insulinoma responds to a further dose of glucagon as shown in Fig 3.

The hyperglycaemia following intramuscular adrenaline and intravenous glucose in these patients does not appear to have the same effect in provoking hypoglycaemia as glucagon. The change in glucose concentration against time, after the peak

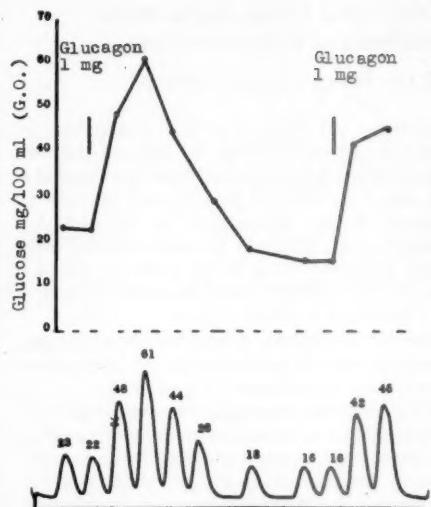


Fig 3 Blood glucose response in one patient to 2 injections of glucagon. Glucose in capillary blood taken at 15-minute intervals was measured on an auto-analyser by a glucose oxidase method (Wincey & Marks 1961) and is shown in the lower half of the diagram. The results are expressed graphically in the upper half and show the glycaemic response to a second dose of glucagon during the hypoglycaemia produced by the first.

of the glucagon-induced hyperglycaemia, closely approximates to a first order reaction and the glucose assimilation coefficient (G.A.C.) (Conard *et al.* 1953, Marks & Marrack 1961) was, in 4 of the cases, greater than that normally obtained with the intravenous glucose tolerance. The G.A.C.s in these 4 cases were similar to those we have obtained by giving insulin with glucose intravenously to control subjects. The significance of this observation is not clear.

Tolbutamide Test

In the tolbutamide test 1 gram of sodium tolbutamide dissolved in 15–20 ml of distilled water is given intravenously and the extent of the fall and the subsequent restitution of glucose concentration in capillary blood is followed for the next three hours. The mean response in 39 control subjects is shown in Fig 4, together with the data from 4 cases of insulinoma. The feature of these cases is the failure of the blood glucose to rise again after the initial fall, i.e. the response to hypoglycaemia is disordered. In normal subjects the blood glucose always returns to at least 70% and usually 80% of the fasting level at three hours.

The findings with this test in various groups of patients in addition to those with insulinoma are shown in Fig 5. The pre-test blood glucose concentration is plotted against the percentage drop in

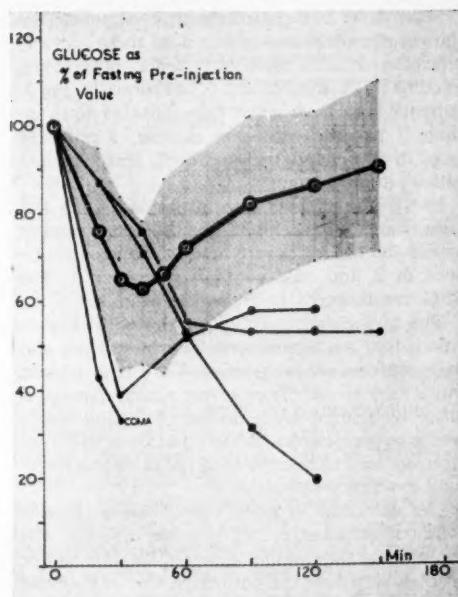


Fig 4 The mean blood glucose response $\pm 2 \times S.D.$ expressed as a percentage of the fasting level, in 39 control subjects given 1 gram sodium tolbutamide intravenously at zero time is shown by the shaded area. The responses in 4 patients with insulinoma, not hypoglycaemic at the start of the test, are also shown

glucose level at 90 minutes after the tolbutamide injection. On such a diagram (Fig 5) controls form a group in the upper right quadrant and patients with insulinomas lie to the left and below.

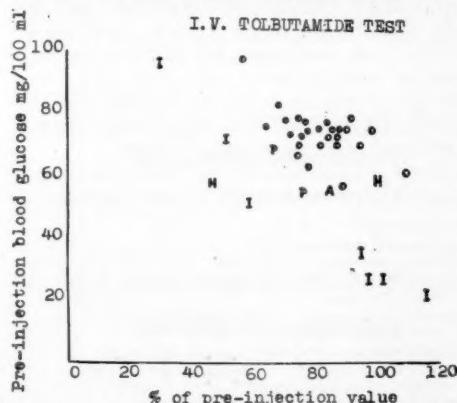


Fig 5 Blood glucose concentration at 90 minutes after 1 gram sodium tolbutamide intravenously, expressed as percentage of the pre-injection level (abscissa), plotted against pre-injection glucose concentration (ordinate). O=control subjects; I=insulinoma; H=hepatic disease with spontaneous hypoglycemia; P=probable pluriglandular syndrome; and A=pituitary adenoma

Seven tests in 6 patients with insulinomas are shown. An additional test in 1 of these patients precipitated acute neuroglycopenia, progressing to coma in 26 minutes and is not shown in Fig 5. Patients who have given false positive tests include 2 patients with liver disease, 2 probable cases of pluriglandular syndrome, and a patient with a pituitary tumour.

In 3 of the patients with insulinoma there was little change in the blood glucose concentration during the test yet severe neuroglycopenia developed in 2, and mild neuroglycopenia in 1. The EEG was abnormal in the patient examined.

One of the diagnostic difficulties with insulinoma is that the tumour usually grows slowly and the symptoms are progressive. The advanced case which may already have severe neural damage is easily recognized by a period of fasting which causes hypoglycaemia. But even in these cases the fast may need to be continued for as long as forty-eight to seventy-two hours.

The detection of early cases, before there is neuronal disorganization, is more difficult. The above tests seem to offer a partial solution to this problem and have the advantage that in doubtful cases they can be repeated after a suitable time interval.

The glucagon and tolbutamide tests appear to test two different aspects of glucose homeostasis and we believe that they have a useful role to play in the screening of patients suspected of insulinoma.

Acknowledgments: We should like to thank the Physicians of the National Hospital, Queen Square, and the Atkinson Morley Hospital for permission to study patients under their care; also Drs J Anderson, S Mason, A Paton and M Turner for their help and permission to report the findings on patients under their care. One of us (V. M.) wishes to thank the Medical Research Council for a clinical fellowship during tenure of which part of the work was carried out.

Glucagon was supplied by Messrs Eli Lilly & Co, and tolbutamide by the Upjohn Company.

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A New Oral Progestogen in the Treatment of Dysmenorrhoea

by P M F Bishop DM FRCP (London)

An entirely new series of steroid compounds has been recently synthesized by Reerink and his colleagues in which the stereochemical configuration has been altered by reversing the spatial position of the substituents at C₉ and C₁₀ (Reerink *et al.* 1960). In progesterone the angle methyl group at C₁₀ is in the β (or *cis*) position whereas the hydrogen atom attached to C₉ is in the α (or *trans*) position (Fig 1A).

The corresponding compound (*retro*-progesterone) in the new series is the 9β, 10α stereoisomeric analogue (Fig 1B).

The 6-dehydro-derivative has been found by Schöler (1960) to be a pure progestational compound with no oestrogenic or androgenic properties. It has been given the trivial name of isopregnene and is shortly to be marketed under the trade name of Duphaston (Fig 1C).

A study of the human pharmacological properties of isopregnene as a progestational agent was carried out in the Department of Women's Diseases of the Karolinska Sjukhuset in Stockholm by Dr Egon Diczfalussy and Dr Tillinger, in the Department of Obstetrics and Gynaecology of the University of Göteborg by Professor Ulf Borell and in my Department at Chelsea Hospital for Women. It was shown that this compound induced classical progestational transformation of the oestrogen-primed endometrium in castrated women and in cases of primary and long-standing secondary amenorrhoea. The results of these human pharmacological studies will be published in due course (Bishop *et al.* 1961). The present communication concerns the effect of isopregnene in dysmenorrhoea.

We have selected for our trials only patients complaining of 'incapacitating' dysmenorrhoea, that is pain sufficiently severe to keep them in bed, absent from school or away from work and occurring in practically every cycle. At least 75% of these patients had received previous treatment such as dilatation of the cervix, antispasmodics, analgesics or sedatives without appreciable effect.

In 1940 Sturgis & Albright suggested that spasmodic dysmenorrhoea was due to the presence of endogenous progesterone and could be prevented in any menstrual cycle by inhibiting ovulation. For many years this has been successfully achieved by suppressing pituitary gonadotrophin release with oestrogens administered in the first half of the cycle (Bishop & Ortí 1952). Pincus and his colleagues (1958) showed that orally active progestational agents, such as norethynodrel, can inhibit ovulation and therefore act as contraceptives, by

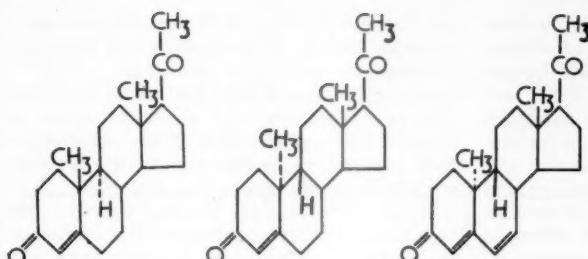


Fig 1A, Progesterone Fig 1B Retro-progesterone Fig 1C Isopregnенone

suppressing the release of gonadotrophins from the pituitary, when administered from the 5th to the 25th day of the menstrual cycle.

In planning our studies on the effect of isopregnенone on dysmenorrhoea we therefore presumed that, if successful, it would prevent the pain of the subsequent menstrual bleeding by inhibiting ovulation. We consequently decided to give the compound daily from day 5 to day 25 of the cycle. Because little was known about the effective strength of the preparation when administered to women the dosage varied between 1 and 30 mg. On analysing the results in a group of 44 dysmenorrhoeic women treated for a total of 85 cycles we found a significant dose-response relationship, the optimal daily dose being 15 mg. 'Break-through' bleeding, that is, bleeding beginning during the course of treatment instead of after its withdrawal occurred in 21 cycles and, although it was painless in 18 and therefore gratified the patients, we eliminated them in calculating our final results (Table I).

The results are divided into failures, in which the subsequent period was accompanied by incapacitating pain, and successes, in which the period was either painless or else accompanied by discomfort which, however, was not incapacitating. In fact 35 out of the 47 cycles in this group were completely painless. In order to simplify the presentation of our results I have separated the cycles into two dosage groups only, those in which 10 mg was given daily and those in which 15 mg or more was given. In the first group one patient received 5 mg and in the second 29 received 20 mg, but the success rate was exactly the same whether the daily dose was 15 mg or 20 mg. The overall success rate was 73%, 63% on the 10 mg dose and 82% on the dose of 15 mg or more. Isopregnенone therefore prevents spasmodic dysmenorrhoea in a high percentage of cases when given in 15 mg doses or more from the 5th to 25th day of the cycle. Furthermore in our experience of over 4,500 treatment-days there were no unpleasant side-effects.

Early in our trials we found that isopregnенone

Table I
Effect of isopregnенone on the subsequent period in cases of dysmenorrhoea

Daily dose	10 mg	15 mg or more	Total
'Incapacitating' pain	11	6	17
Painless or not incapacitating	19	28	47
'Break-through' bleeding	12	9	21
Total	42	43	85

Final assessment:			
'Total' minus 'break-through' bleeding	30	34	64
Proportion of 'painless' to 'total'	19/30	28/34	47/64
Percentage success	63%	83%	73%

does not raise the basal body temperature as endogenous pregestational agents do. Basal temperatures were recorded daily in 31 of the treated cycles that resulted in painless periods and, much to our surprise, the temperature pattern was certainly or doubtfully biphasic in 23, though probably or undoubtedly monophasic in 8. This suggested that, in some cycles at any rate, the pain can be prevented even though ovulation is not inhibited (Fig 2).

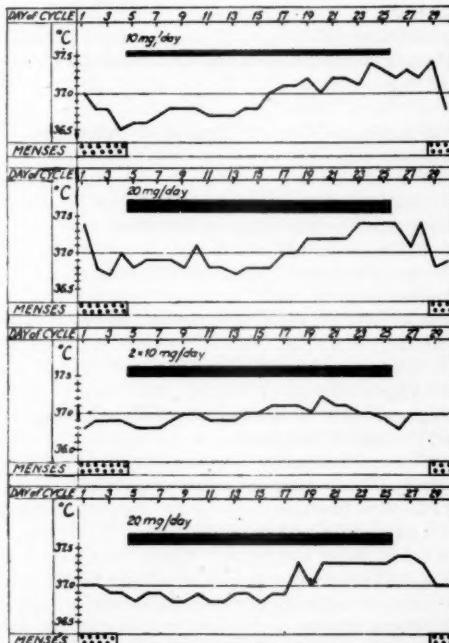


Fig 2 Four consecutive cycles in a normally menstruating woman treated with varying doses of isopregnенone by mouth from the 5th to 25th day of the cycle. Daily basal temperature records indicate that ovulation is not inhibited

It is unwise, however, to rely solely on basal temperature patterns as an indication of whether ovulation has occurred. Diczfalusy and Tillinger therefore estimated the urinary oestrogen and pregnanediol output in 2 successive 28-day cycles in 6 women, not necessarily suffering from dysmenorrhoea. In the first cycle no treatment was given whereas isopregneneone was administered in doses of 10 to 30 mg daily from the 5th to the 25th day in the second cycle. No significant difference was found in the treated and untreated cycles. (It had previously been established that isopregneneone is not excreted as pregnanediol.) These studies also suggest therefore that in these doses isopregneneone does not inhibit ovulation.

Finally Borell administered isopregneneone in doses up to 40 mg daily from the 5th day onwards to 12 women who were due to be operated upon in the cycle in which the treatment was being given. The ovaries were inspected between

the 18th and 23rd day. In 10 cases the presence of a freshly formed corpus luteum was confirmed histologically, whereas in another case a recently ruptured Graafian follicle was identified. In the 12th case a follicular cyst was removed but no luteal tissue was identified. These observations fully support the contention that isopregneneone, in these doses, does not inhibit ovulation.

In the light of these findings it seems that current views concerning the hormonal factors in the causation of spasmodic dysmenorrhoea may need reconsideration.

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(Meeting to be continued)

Meeting February 22 1961 continued from p 747

The following papers were also read; they will be reported in the *Journal of Endocrinology*:

Endocrine Relations of the Pregnancy 'Syndrome' in Mice

Dr A D Dewar

Effect of Hysterectomy on the Ovaries of Rats and Pigs

Dr J S Perry

Maintenance of Corpora Lutea by Hysterectomy in Guinea-pigs

Dr I W Rowlands

The Half-life of Progesterone in the Blood of Sheep at Various Stages of Gestation

Dr R V Short and Dr J G Rowell

Hormonal Control of Myometrial Function

Dr Brenda M Schofield

Oestradiol and Pregnaneadiol Excretion During Pregnancy and at the Onset of Labour

Mr A Klopper, Mr M C Macnaughton and

Mrs Eileen A Michie

Pregnaneadiol Excretion in Placental Insufficiency and Prolonged Gestation

Professor C S Russell

Urinary Oestradiol Determinations as an Index of Placental Function

Mrs Valerie K Cartilage, Mrs Pamela M Spencer,

Dr G I M Swyer and Mr A J Woolf

Pregnaneadiol and Oestrogen Excretion in Cases of Abortion and Intra-uterine Foetal Death

Dr Mary G Coyle

Spontaneous Uterine Activity with Relation to the Sympathetic Nervous System

Dr Mary Pickford

Blood Concentration of Oxytocin in Labour

Dr R J Fitzpatrick

Tocographic Studies of the Effects of Neurohypophyseal Hormones in Pregnancy and Labour

Mr M P Embrey

Present State of Relaxin Studies

Dr Kathleen Hall

Tocographic Studies of the Effect of Relaxin in Pregnancy and Labour

Mr M P Embrey

Meeting May 24 1961

The following cases were shown:

Primary Hyperparathyroidism Presenting as Arthritis

Dr D White and Dr I Gilliland

Two Cases of Diabetes Complicated by Charcot's Arthropathy

Dr E A Dodge (for Dr A Bloom)

Cushing's Disease and Vitiligo

Dr D G Martin (for Dr R Greene)

(1) Cushing's Disease Treated by Needle-implantation of Gold-198 Seeds into the Pituitary Gland, without Causing Hypopituitarism

(2) Virilism Due to Hilus Cell Tumour of the Ovary
Dr G F Joplin and Dr Russell Fraser

Diffuse Systemic Sclerosis, Treated with Relaxin

Dr J Arnold (for Dr D Ferriman)

Hypothermic Coma Probably Due to Hypothalamic Infarction as a Result of Cerebrovascular Syphilis

Dr C W H Havard (for Dr A W Spence)

United Services Section

President E R Boland CBE FRCP

Meeting December 19 1960

Papers

Visual Problems under Water

by Surgeon Lieutenant E E P Barnard MB MRCS
LRCP (Royal Navy)

Replacement of air by water at the corneal surface produces a gross hypermetropia due to the loss of about two-thirds of the refracting power of the eye. Visual acuity is reduced from 6/6 to less than 1/60. To restore normal vision under water, masks or goggles, which replace the air at the corneal surface, and lenses containing air cells have been used.

The former are both older, most used and most successful, but diving masks have almost completely replaced goggles since masks give a better field of vision. Masks restore normal refraction to the eye by restoring the air-corneal interface but produce a refraction at their outer surface which has three secondary effects: (a) Narrowing of the visual fields due to the incident ray being refracted away from the normal on entering a less dense medium, (b) the magnification of objects, which upsets judgment of size and distance, and (c) a less important effect, the distortion of verticals and horizontals.

The visual field underwater is usually described as being three-quarters of the field in the air (Tailliez et al. 1955). It is given precisely by the ratio

$$\frac{\text{angle of incidence}}{\text{angle of refraction}} = \left\{ \frac{i}{r} \right\}$$

For an incident angle of 1 degree from the

$$\text{normal this ratio} = 0.75 \left\{ \frac{i}{r} = \frac{1^\circ}{1^\circ 20'} \right\}$$

But for an incident angle of 48 degrees the ratio

$$= 0.59 \left\{ \frac{i}{r} = \frac{48^\circ}{81^\circ} \right\}$$

(For simplicity in these calculations the refraction due to the glass or perspex of the mask has been neglected.)

At 48·6 degrees (the critical angle) light rays are

totally reflected from the water-air interface. This phenomenon of total internal reflection sets a limit to the cone of vision which can be obtained through a plane surface in any underwater visual aid.

Magnification: Since the ratio of $i : r$ decreases as the rays become more oblique, the apparent displacement of objects seen increases as their angular diameter increases. This magnification leads to mistakes in judgment of either size or distance, but with experience these are quickly overcome.

Distortion depends on the angular diameter of the object and is most noticeable with uprights or horizontals which are not in the normal plane. A 'pin-cushion' deformity is produced.

A series of trials have been carried out to test underwater contact lenses. McLintock (1950) used a double lens with a conical anterior surface and containing an air-space. This was a development in more modern terms of the underwater spectacles suggested by Valentine (1924).

Subsequently, chambered lenses with a plane anterior surface were tested. It was argued - from measurements of a half-field of 75 to 80 degrees in air - that they would be superior to a mask in water. These lenses, however, must be subject to the same limitation as the masks, that the field cannot exceed about 96 degrees, or 48 degrees for a half-field, when immersed in water. Glass (1958) modified the lenses by the inclusion of a tantalum gauze filter in the fenestration.

Tests of Diving Masks

Preliminary results have been obtained with an underwater perimeter. A sea-cell was used to produce a 2 mm light source contained in a manually operated box running on rails made by the perimeter arc.

We have used a plastic hemisphere lent to us and designed by Rubens (1951). This was convenient for measurements in air, but the diving

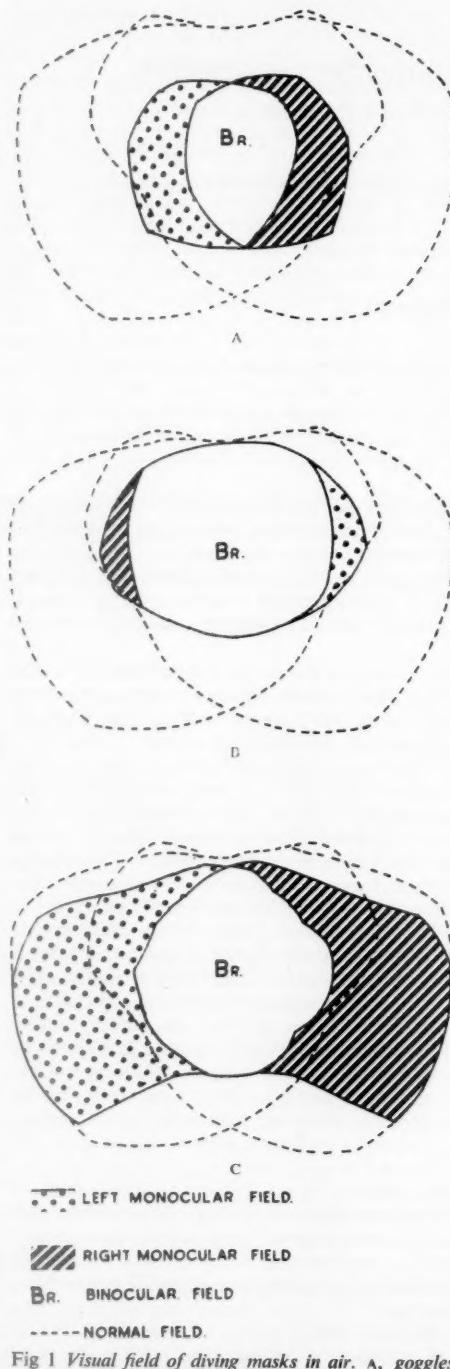


Fig 1 Visual field of diving masks in air. A, goggles.
B, swim-mask. C, wide-vision mask

gear tended to foul the perimeter. A light source enabled simple plotting of binocular fields using red and green spectacles worn under the diving masks.

Goggles: give small monocular fields and a small binocular field. There is a tendency for fusion to break down, producing diplopia, particularly if the front glasses are not in the same plane. The 'blinker' effect was also noticed, the lateral part of the field being reduced on lateral movement of the eye (Fig 1A).

Swim-mask: Most of the field is binocular; the 'blinker' effect is shown by the appearance of crossed monocular fields (Fig 1B).

Wide-vision mask: This gives a good binocular field and apparently wide monocular fields. However, in water most of the monocular field is grossly distorted due to the curvature of the mask (Fig 1C).

Size of the Field

Perimetry confirms the reduction of the visual fields under water by approximately the expected amount. Dugan (1960) quotes South Sea divers as claiming that their vision is 'greatly improved' at about 100 feet below the surface, when diving without masks. The same claim has been made by two of the Instructors at the Submarine Escape Tank, H.M.S. *Dolphin*. Dugan, a journalist interested in diving, attributes this improvement to 'flattening of the eyeballs'. Whether such an improvement can take place in an emmetrope is still uncertain. Tests with standard visual acuity charts appear to show a slight improvement – that is, the second line could be read at 12 cm at the surface and the third line at about the same distance at a depth of 30 metres.

Present charts are not suitable for the testing of such poor grades of vision. It is hoped to use a modification of Landolt's rings with movable symbols to make identification depend more on vision and less on memory.

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- Rubens M (1951) *Brit. J. Ophthalm.* 35, 634
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The following papers were also read:

Ophthalmic Practice in the Navy

Surgeon Captain D P Gurd (*Royal Navy*) (see Klein M (1956) *Trans. ophthal. Soc. U.K.* 76, 223)

Visual Problems in the Fleet Air Arm

Surgeon Lieutenant-Commander W A N Mackie (*Royal Navy*)

Meeting March 23 1961

Papers

The Central Sterile Supply Service of the Cambridge Military Hospital, Aldershot

by Lieutenant-Colonel J M Matheson OBE MD MRCP FRCSED (Royal Army Medical Corps)

The history of the development of Central Sterile Supply Services (CSSSs) in the Army probably stems from the difficulty of sterilizing dressings in the field, for this led, in 1942, to the formation in Cairo of a Surgical Dressing Sterilizing Unit (Matheson 1945).

After the Second World War the Army Medical Services renewed their interest in central sterilization for the improvement of sterilizing practices. In the meantime, the past decade has been notable in this country for the emphasis given to the causes and prevention of hospital sepsis. Criticisms of sterile techniques and of faults in the design and operation of sterilizing apparatus, and remedies, have accumulated in the literature, many ultimately being embodied in the reports of the Nuffield Provincial Hospitals Trust (1957, 1958) and of the Ministry of Health (1959). By this time Central Sterile Syringe Services had been established in some civilian hospitals and a few had begun to develop Central Sterile Supply Services.

CSSSs have been established in most military hospitals at home and overseas for some time and vary very much in their development and scope. The one which has expanded most and has the largest commitment is that at the Cambridge Military Hospital, Aldershot; it started on a modest basis a number of years ago and by 1955 was established as a unit for research and development in this field. A Central Sterile Syringe Service having been started, the Hospital autoclaves were then taken over to supply the sterile packs for operating theatres and wards. It then undertook the supply of syringes and packs to the adjacent Louise Margaret Maternity Hospital and to camp hospitals and medical centres in the Aldershot area. A major outside assignment giving valuable experience came in 1956 when, at short notice, the CSSS had to prepare operating packs for field surgical teams proceeding to the Suez Canal.

A description of the CSSS was published in an Army Medical Directorate Bulletin (1960) and although the principles it outlined still held, the organization and packs described had been significantly modified by the summer of 1960 when an automatic high-vacuum steam sterilizer had been installed and when the task of supplying two military hospitals and medical centres in the London area was undertaken.

By 1960 the benefits of a civilian CSSS project had been established in terms of economy both of nurses' time and financial cost (Darmady *et al.* 1960), and CSSSs had become an accepted feature of civilian hospital planning.

The Cambridge Hospital CSSS now produces some 1,200 sterile syringes and over 400 sterile packs daily to meet the needs of five army hospitals comprising in all some 1,100 beds, six camp hospitals within a radius of 25 miles, and 65 medical centres varying in size from mere consulting rooms to reception centres with beds; also troopships plying from Southampton, and field medical units when proceeding on exercises or operations. Apart from the Louise Margaret Maternity Hospital which is adjacent to the Cambridge Hospital, the other hospitals vary in distance, viz. the Connaught Chest Hospital (15 miles), the Queen Alexandra Military Hospital, Millbank (40 miles), and the Royal Herbert Hospital, Woolwich (50 miles).

Organization

The CSSS is responsible for the production of the sterile requirements of wards, theatres and medical centres other than theatre instruments and pharmaceuticals. It is under the control of the Officer i/c Surgical Division who is a member of the hospital control-of-infection committee. The Supervisor is a Warrant Officer Class II RAMC who is a State Registered Nurse and has been selected for his administrative ability and for his experience in ward and theatre work. He has also been carefully trained in sterilizing procedures. He has a staff of ten persons including RAMC personnel and civilians. Among the

RAMC is an NCO who looks after the accounting and stock. The responsibilities of each person, especially those who work the sterilizing apparatus, are clearly defined and supervised. The Hospital pathologist is the monitor of the sterilization standards in the department.

Accommodation and Apparatus

The CSSS is accommodated in a small ward suite on the main floor of the hospital near the operating theatres. The ward has been adapted to provide a storeroom, supervisor's office, large packing room, autoclaving room, syringe processing room and sterile pack store. The rooms are furnished so as to allow an even flow of work. The autoclave room has a 15 cu. ft automatic rapid high-vacuum steam sterilizer and four gravity displacement autoclaves, one of which is used for bottled non-injectable theatre fluids. The syringe room has syringe-brushing and needle-washing machines and hot-air ovens.

The Hospital does not have its own laundry and depends on contracts with two civilian laundries for a weekly laundry service.

Syringes

Syringes used are of the British Standard non-interchangeable all-glass Luer pattern. Each

syringe is packed in an extruded aluminium container with cap, using a protective silicone rubber ring round the shoulder of the syringe barrel (Fig 1). Needles supplied are 1 in. (23 SWG) and 1½ in. (21 SWG). Damaged and blunt needles are discarded. Depending on the preference of the user, syringe needles are included in the metal containers or packed separately in glass tubes.

Syringes are washed with a soapy solution on a syringe-brushing machine and then rinsed. Needle hubs are cleaned with a cotton-wool covered dental burr and their shafts are cleaned by a water injection device. Syringes and needles are sterilized in hot-air ovens at 160°C for two hours.

Packs

All articles used in packs are capable of withstanding the sterilization process, storage and handling. They are packed to ensure sterility and ease of use on opening. Fig 2 illustrates the sequence of work in the packing room.

Most drums have been discarded and replaced by a range of under a dozen sizes of cardboard boxes which are easy to replace, stack, autoclave and transport. Cardboard boxes are sealed with an adhesive indicator tape which is pressure- and heat-sensitive and develops, in a satisfactory autoclave process, diagonal tan coloured lines. This tape serves as an indicator of sterility to pack users.

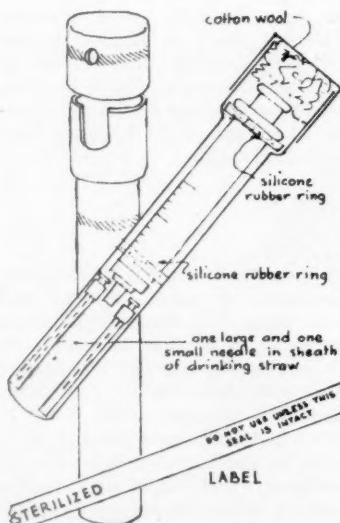


Fig 1 Duralumin syringe container

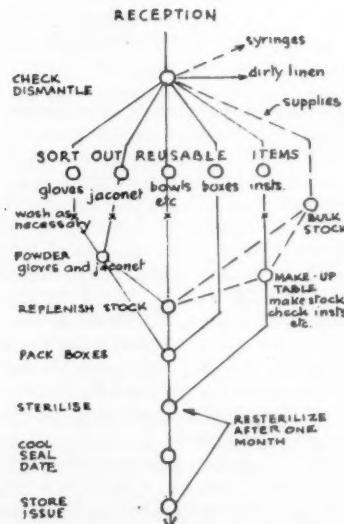


Fig 2 Job sequence - pack room



Fig 3 Contents of intermediate size operating pack

Each autoclave load of packs includes one or two dummy test packs, each containing a Browne's control tube wrapped in a towel, and no sterile packs are issued unless the Browne's tube has changed colour satisfactorily. After autoclaving all packs are stamped with the date of sterilization. The autoclaving of packs is usually completed during the day shift.

For long journeys in this country, and for overseas, autoclaved packs are either individually wrapped in polythene sheeting or packed in air-freight plywood boxes lined with polythene sheeting. For theatre use and special clinical procedures, the cardboard boxes serve solely as contain-

ers, their contents being securely parcelled up in a relatively dustproof and waterproof cotton duck canvas material which also replaces jaconet or rubber sheeting as a trolley top cover when the packs are opened for use.

A variety of packs for all clinical and theatre procedures is made in the CSSS and they range from the more elaborate packs for major operations (Fig 3) and obstetric deliveries (Fig 4) down to small paper bags each containing two swabs or two cotton-wool balls. The composition of packs has undergone much modification and the trend has moved away from elaborate, bulky and comprehensive packs which were tedious to assemble and tended to contain more than was necessary. Smaller 'unit' or 'basic' packs have been devised to provide the least number of items common to many procedures. It is also worthy of note that at least a dozen surgeons in various specialties, and their theatre sisters, have been using the three sizes of basic operating packs provided. Apart from operating gown and linen packs the most popular packs have been dressing packs (Fig 5) and so-called 'Medical Centre Packs' for unit medical officers. The latter contain five paper bags of which two each contain 10 sealed packs of two gauze swabs, two other bags each contain 10 sealed packets of two cotton-wool balls and the remaining bag contains three sealed packs each with a cotton-wool pad (6 in. x 4 in.). The Army Medical Equipment Depot (AMED) at Ludgershall, Wilts., has, during the last few months, been packing most of the simpler disposable packs of dressings. Dressing instruments are supplied separately in tins and are sterilized in hot-air ovens. Gloves are separately autoclaved in paper folders and packed in pairs in boxes.



Fig 4 Emergency obstetric pack



Fig 5 Ward dressing pack

Difficulties

Some factors have affected smooth working of the CSSS. In the first place the rate of expansion of the service has, at times, outstripped supplies. Accounting for stock has been difficult with so much equipment packed and coming and going, but some check has to be kept of returned packs as items do get mislaid, like operating towels, kidney dishes, and silicone rubber rings for syringes; some, like scissors, can get misappropriated and a disproportionate amount of time is spent in tracing them, often in vain.

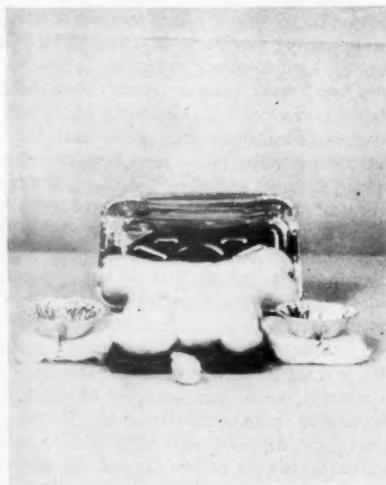


Fig 6 Disposable dressing pack

Then, trying to maintain a daily service of a large range of packs containing gowns, operating sheets and towels with only a twice weekly laundry change inevitably leads to occasional shortages. In addition the inspection and refolding of laundered operating linen and gowns is a time-consuming activity in the CSSS. Our automatic rapid high-vacuum autoclave has not been as automatic as anticipated and has required frequent engineer and manufacturer's attention for breakdowns due to such causes as leaking door seals, trouble with the door-locking mechanism, moisture contamination of the oil-sealed vacuum pump, and failure of the micro-switch of the automatic system. These have all caused anxiety when a crowded timetable has had to be adhered to.

Fluctuations in strength and changes in CSSS staff have also made the Supervisor's task an exasperating one. Errors have occasionally been committed by inexperienced staff, only to be revealed when the packs or syringe containers were opened for use, causing much annoyance to users.

Research and Development

Much time and energy has been spent in trying out new methods, apparatus, materials for packaging and substitutes for linen and dressings, disposable and otherwise. The rapid expansion of the service, coupled with changes in staff, materials and methods, has prevented the assessment of comparative costs and savings. Capital and running costs may well have been high during the period of expansion.

Kidney dishes, gallipots and instruments like syringes and needles, when returned to the CSSS, are washed by hand and with the increasing work load some labour-saving apparatus will be required to reduce the large handwashing commitment especially for syringes and needles with the present daily commitment of 1,200 syringes. Consideration has been given to the merits of the ultrasonic cleaner and the Heinicke automatic washing machine but it has been decided that the capital outlay involved in purchasing either of these expensive machines might be avoided by the adoption, at least, of disposable needles which would abolish the worst chore, namely, the tedious inspection and cleaning of hundreds of needles.

Disposability, where possible, and with due thought to economy, is a constant aim in our Central Sterile Supply Service development as the handling of contaminated used items would thereby be eliminated.

Disposable syringe devices have been in use for some time in the Army: 'tubunic' morphia syringe

devices have been used in the field, and dental officers have been using another syringe with a disposable loaded cartridge and needle. There is undoubtedly scope for the use of disposable syringes or syringe substitutes and trials are being carried out using disposable pre-sterilized loaded injection devices for the more commonly administered drugs such as penicillin and premedication drugs which form a large proportion of the injections given in surgical wards.

Disposable paper caps and masks are available but have not met with universal acceptance by our surgeons although the nursing staff have been more receptive. The surgeons' objection to the masks, which are made of absorbent paper, is that they tend to become like blotting paper over the mouth and nose during a long operation in a warm theatre and that the elastic irritates the ears.

Though a disposable operating theatre gown has yet to be tried, several types of disposable paper and cotton waste operating towels have proved useful and are being tried out at home and overseas in operating and ward dressing packs (Fig 6). Aluminium trays and gallipots in disposable ward dressing packs are already in use. Tubes and catheters have always been difficult to clean and disposable equivalents have been readily accepted.

In June 1960 a small number of senior army surgeons met under the Director of Surgery and agreed on the contents of a limited range of operating and dressing packs (designated as 'interim universal packs') which could be used in hospitals or in the field. So far the reports received on the use of these packs have been favourable.

It is hoped in due course to produce a standard range of disposable packs and that they would be packed, sterilized, and issued in bulk from the AMED, Ludgershall. In due course, the AMED, Ludgershall, will be able to carry out its own steam sterilization but an increasing use of gamma-ray sterilization is contemplated. Gamma-ray sterilization has been explored for our needs especially as it has enabled disposable dressings to be compressed, thus saving bulk, and wrapped in sealed plastic envelopes which have seemed to withstand handling, insects and hot, humid or dry climates better than drums or cardboard boxes. The radiation process has been carried out at the Wantage Radiobiological Laboratory and the plastic envelopes have incorporated, in a sealed corner, an indicator which has a red colour after irradiation.

If current and planned world-wide trials of irradiated disposable packs and disposable

syringe devices are successful and approved financially, a new phase in the development of CSSSs will open: the work of army hospital CSSSs, and of the Cambridge Hospital in particular, will be drastically reduced and confined to the preparation and heat sterilization of a few selected items and to their distribution. It is possible that irradiated disposable packs like commercially produced sterile intravenous fluids, may be issued through pharmacies.

CSSSs have arisen from the difficulty of sterilizing in the field and dissatisfaction with sterilization discipline. They have led to safety and economy of time and materials and it is hoped that the care taken to achieve these standards will be reflected in a general improvement of aseptic techniques.

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The Nurse and the Central Sterile Supply Service

by Major J M Orford

(*Queen Alexandra's Royal Army Nursing Corps*)

The Central Sterile Supply Service at the Cambridge Hospital has been established for some years and the attitude of the nursing staff to it is, in general, a healthy one, and, if anything, it has been taken for granted, as have commercially prepared drugs and intravenous fluids. The nursing staff have developed confidence in the standard of sterility of the items supplied, a standard which could not be maintained in the wards using traditional boilers and drums, and in the adequacy of the supply of the items.

The Ward Sisters have the opportunity of visiting the CSSS and appreciate the close supervision maintained by the Supervisor on the sterilizing standards. The sealing of the sterile packs with indicator tape has helped in the acceptance of these standards.

With the ready supply of sterile materials the nurse has no longer to devote time to the boiling of apparatus for sterile procedures and especially of

reboiling between dressings. The system has also eliminated the temptation to take short cuts with boiling. No longer has she the task of packing dressing drums nor the opportunity of repeatedly reopening the same drum for dressings for different cases. Incidentally, also, no longer is the atmosphere of the treatment room misty and dank with the steam from the boilers and, indeed, the burnt-out boiler is also a thing of the past. Of course, there is still cleaning up to do after the dressing or other procedure but here, too, the system has been facilitated by the provision of paper bags for the disposal of used items. The amount of time saved is difficult to estimate and to reduce to hard terms of man-hours though it has been estimated by Darmady *et al.* (1960) to be between two and a half to three hours daily. Although we tend to suffer fluctuations and shortages of staff, we do have at the Cambridge Hospital the benefit of a recovery ward and also of a septic ward which concentrate nursing and dressing tasks and contribute towards the amount of time saved in other wards. Nevertheless, Sisters are definite that with the CSSS system they have more time for individual bedside care and for active nurse training. Two other benefits of the system should be mentioned. First, the instruments are undoubtedly in a better state of maintenance by repeatedly going back to the CSSS for cleaning and inspection and sterilization and, secondly, there is much less tendency to hoard apparatus against emergencies in the wards.

If what I have said suggests that the nursing staff have invariably been satisfied with the CSSS, nothing could be more untrue, for difficulties and misunderstandings have occurred during its development, but from these have stemmed improvements and better understanding. Annoying deficiencies in packs, blocked syringe needles and defective connexions have occurred and have threatened to undermine confidence in the system. These have been traced to unreliable and inexperienced packers, but at the same time, they have also revealed that nurses have not been blameless in failing to wash out syringes after use or to ensure that used apparatus has been returned complete in all its components.

In the training wing at the Cambridge Hospital sterile packs are used from the CSSS for the various procedures which are required to be taught to the nurses from a very early stage in their training. Unsterile instruments, boilers and drums are, however, also shown to acquaint nurses with them and to emphasize the reasons for their unreliability and so that they will know how to use them properly especially in situations where a CSSS and pre-sterilized apparatus may

not exist or when pre-sterilized supplies may be interrupted.

Student nurses in our Army Preliminary Training School all visit the CSSS and spend an afternoon being shown round by the Supervisor. During the first year of hospital training they spend one or two afternoons in the CSSS, studying its sterilizing procedures and standards. During the course of their second or third year, student nurses spend a fortnight in the CSSS learning its various activities, including methods of cleaning, packing and distribution. This has been found to be a sufficient exposure to Central Sterile Supply Services. One virtue in the use of pre-sterilized apparatus is that emphasis in teaching and practice can be put on other aspects of anti-cross-infection measures. The measures being taken to improve sterilizing practices and to eliminate sources of cross-infection cause one to wonder if a great deal of what has been accepted in the past as good aseptic technique is not so much meaningless 'mumbo-jumbo' and whether such ritual as swabbing first-intention wounds with antisepsics before and after removal of sutures could not be discarded. It is hoped that accepted drills will, with modern developments, be further revised and modified, leaving the nurse more time and energy for her real function of promoting the physical and psychological well-being of her patient, and giving her more opportunity of learning at the bedside the skills of her profession.

Treatment of Used, Soiled and Contaminated Linen

Operating towels, sheets and abdominal swabs require sluicing in water to remove stains. This has to be done by the nurses and is recognized as an infection hazard. The sluiced linen and other used linen is collected in sealed bags and taken to the disinfector before being counted out for despatch to the laundry. The use of large disposable paper bags for used linen is a great help but it would be better if the sluicing by nurses were replaced by sluicing in a central washing machine (as is done at St Mary's Hospital, Portsmouth: all used linen there is placed in paper bags and taken to a central place where it is emptied into an automatic washing machine in which it is first tumbled for ten to twenty minutes in cold water to remove stains and then rinsed in a disinfectant solution. After this it is placed in a spin dryer and then counted before dispatch to the hospital laundry). Nurses will welcome disposable packs to eliminate the sluicing of soiled linen and its possible infection risk.

Trials with disposable packs have been carried out and have been favourably commented on by the nursing staff. By the time they come into regular use, nurses will have been trained in a drill to ensure that the principles of asepsis and economy are observed. In evolving this drill it is intended to discard the use of Cheatle's forceps. With the present ward-dressing pack these are used to remove towels and other items from the cardboard box. This is known to be a source of contamination as the sterilization and storage of these instruments is doubtful. We experimented with a pack wrapped in duck canvas which, when lifted out of the container could be undone readily and opened out to provide a sterile field on a trolley. However, it was found that with the metal receiver and gallipots the package was too bulky to be satisfactory. With the provision of disposable towels and aluminium foil containers, this difficulty will be overcome and the outer wrapper of the pack will be folded to facilitate opening, thus rendering Cheatle's forceps unnecessary. The introduction of disposable tubes and catheters is a great advance, for the cleaning of rubber catheters and tubes even in careful hands leaves much to be desired.

The so-called 'clean' wool mops and gauze swabs used on wards for unsterile nursing techniques are being eliminated. In the past it has been customary to store these in glass jars. Gradually Ward Sisters are being persuaded to use swabs provided in packets of units of two mops from CSSS. In our recovery ward paper tissues are provided for post-anesthetic trays.

While the Central Sterile Supply Service has been accepted and has facilitated the work of the nursing staff, a strange situation arose in connexion with nurse training. For a while the student nurses were somewhat confused by practising a routine with pre-sterilized packs and syringes in the wards when, at the same time, they were being taught traditional boiling and laying-up by the Sister Tutor for nursing examinations. It was no wonder that they began to imagine that there were two very distinct ways of preparing for aseptic procedures, one peculiar to the Army and the other peculiar to examinations and probably to civilian hospitals, and were getting the impression that they might be handicapped in their training by using CSSS packets and sterile syringes. The situation has now, fortunately, been clarified, first by the knowledge that examining bodies will accept laying-up using sterile packets, as well as from unprepared apparatus and, secondly, that the CSSS comprehensive packs themselves have been broken down into smaller denominations.

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(1960) *The Hospital*, Oct. p 2

DISCUSSION

Lieutenant-General Sir Alexander Drummond

This discussion on the Central Sterile Supply Service has closed an era of the system which has become outdated. As a result numerous pilot schemes to form a world-wide service have been tried out.

The projected new organization is centred in the Army Medical Equipment Depot, Ludgershall, Wilts., and the Radiobiological Laboratory at Wantage.

Hospitals and medical units, however, will still be responsible for sterilizing their own theatre instruments.

Syringes: Sterilization of syringes in hot air ovens continues in individual hospitals; the norm should be that each syringe should be used and sterilized at least three times per day.

The introduction of Ampins in military hospitals for pre- and post-operative medication and for antibiotics is already reducing the syringe requirements. Ultimately this reduction should amount to 75% of the present syringe requirement.

Linen gowns and sheets: Until economically priced disposable articles are available these will be sterilized in conventional autoclaves. The work is, however, divorced from the operating theatre and its staff. Where possible it is centralized in one for a number of hospitals.

Gamma-ray sterilization: Dressings, individual and for operating theatres; disposable operating towels and sheets for field force units suitably packed in paper or plastic bags and compressed are subjected to partial vacuum before heat sealing and sterilization by gamma rays. The packs are then despatched world wide.

The Army has started with a capacity requirement of 200 cu. ft per week. This will increase to 250 cu. ft per day.

Manpower saving in the new system is considerable.

The following paper was also read:

The Distribution of Sterile Supplies
Warrant Officer II S R Collantine SRN
(*The Royal Army Medical Corps*)

Meeting June 29 1961

Paper

George James Guthrie, Peninsular Surgeon

by Colonel J C Watts OBE MC FRCS (*London*)

The Renaissance period with its tremendous upsurge of new ideas and its intense vitality was also marked by important changes in the art of war. These changes were reflected in the advances made in military surgery and surgery in general. Maître Henri de Mondeville described the treatment of wounds of the abdomen saying 'The large intestine, if wounded, should be sewn up as a furrier sews a skin, and replaced in the abdomen with the wall sutured'; and he records a successful case. Botallus also described minutely the care of gunshot wounds and, of course, Ambroise Paré stands out as the foremost military surgeon of his time.

In the seventeenth century a period of stagnation set in and the eighteenth century wars, which were largely wars of manoeuvre and siege carried out by small professional armies, allowed the status of military surgery to drop. Ignorant and crude quacks were taken into service at miserable rates of pay and the standard of care of the soldier deteriorated abominably, inspiring Hunter to write 'Little has been written on the subject [of gunshot wounds] and what has been written is so superficial that it deserves little attention'. Hunter himself served as a military surgeon in the expedition to Belle Isle of 1761 and later with base troops in Portugal; but his experience in action was strictly limited. The total casualties he saw were only 73 and he came to the conclusion that correct management of gunshot wounds was complete conservatism until infection was fully established, and amputation should be withheld for at least six weeks. Hunter himself in 1786 became Deputy Surgeon General, but one year before this, on May 1, 1785, George James Guthrie – who was to revolutionize war surgery – was born. Guthrie's great-grandfather had been a military surgeon and served at the Battle of the Boyne, and one of his sons was a naval surgeon, who retired after the Peace of Aachen and set up as a pharmacist selling Emplastrum Lythargyri, later leaving the business to his brother, George James Guthrie's father. The boy received a liberal education and learnt French from an émigré Abbé Noel, which knowledge was to stand him in great stead later on.

Sustaining a severe accident in childhood,

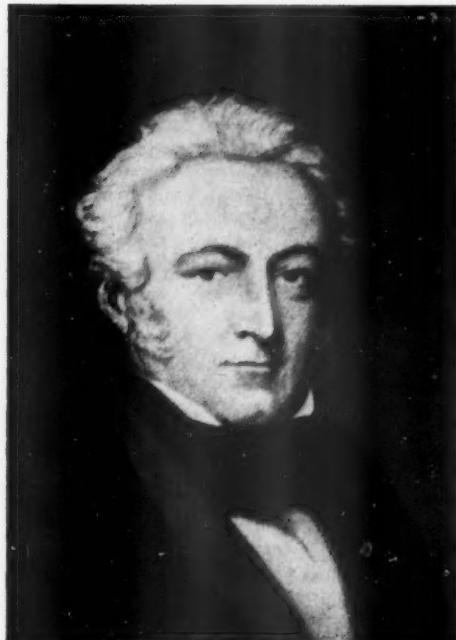


Fig 1 George James Guthrie. Portrait reproduced by permission of the Editor of the Journal of the Royal Army Medical Corps

Guthrie was treated by Mr Rush, Inspector General of Army Hospitals, and perhaps it was this accident and his admiration for his surgeon that turned Guthrie's thoughts to military surgery as a career. So at the age of 13 he was articled to Mr Phillips, the Surgeon, of Pall Mall, and also to Dr Hooper, Physician, of the Marylebone Infirmary; that he made his mark on his teachers is clear from Hooper's saying during his last fatal illness, 'Mind, George, if I am to be cut, you must do it'.

In June 1800 he was appointed as Surgeon's Mate at the York Hospital, Chelsea, where were gathered the wounded from the Helder, and his work on battle casualties began. Meanwhile public concern was growing about the low state of military surgery, made apparent by the numbers of casualties occurring in the Napoleonic Wars, and Charles Bell had petitioned the King to found a Chair in Military Surgery. Within the Services, too, efforts were made to raise the standards and

Mr Keate, the Surgeon General, eventually prevailed on the authorities to introduce regulations demanding that all surgeons' mates pass an examination to prove their surgical competence. In March 1801, therefore, although only 15 years of age, Guthrie passed the examination for Membership of the Royal College of Surgeons and was appointed regimental assistant surgeon and posted to the 29th Foot (later the Worcestershire Regiment), commanded by Lieutenant-Colonel Lord Byng who was aged 23. The Regiment went to America in 1802 where, as *The Times* said, 'notwithstanding the youth of both, it was always admitted that there was no regiment better commanded or doctored'. Guthrie thus had the opportunity to deal with a small number of cases occurring in the guerilla fighting in North America, and there formulated his ideas and developed his skill without the harassing experience of being overwhelmed by the number of casualties or losing sight of the progress of these cases through moves of battle. It was there that he started his practice of immediate amputation in cases where a limb was irretrievably damaged and it was his success in these cases that confirmed his, at the time, revolutionary views, on the importance of early surgery.

In 1807 the Regiment embarked for Ceuta, Guthrie sailing in the *Dominica*. In Gibraltar Bay the ship dragged her anchor and drifted under the Spanish guns in Algeciras. The anchor watch was asleep, but Guthrie detected the unusual movement of the ship, raised the watch, and although under fire from a battery of forty-two pounders and hit several times, the ship managed to get back to her anchorage.

Spain had now rebelled against her usurper King, Joseph Napoleon, so the troops were landed in support of the Spanish near Cadiz, and, whilst there, Guthrie added Spanish to his repertoire of languages.

In August 1808 the Army landed in Mondego Bay under Sir Arthur Wellesley, and the Peninsular War began.

On August 17 the Battle of Rolica was fought, and the bulk of the casualties occurred in the 29th and 9th Regiments, the wounded being under Guthrie's care for three days. Next day at Vimiera the 29th Regiment again suffered severely and Guthrie himself was wounded in both legs by musket ball, but he continued to care for the wounded and he was able to take most of them with him when the Regiment returned to Cadiz. Here he was responsible for all the sick at the base for several months, and, in spite of his arduous duties, he took the oppor-

tunity of learning Portuguese; which useful acquisition enabled him, at the taking of Oporto, to be the first mounted officer to cross the Douro, as he persuaded some boatmen to take him and his horse across. In the confusion of the pursuit of the French Guthrie was separated from his Regiment and found himself with Sir John Doyle's Portuguese Regiment which was mistaken for the enemy by some British troops who, forming into line, prepared to fire; Guthrie realizing what was happening, stripped off his greatcoat exposing his red tunic, and thus prevented what might have been a very unfortunate incident. Later the same day, he saw a French gun being dragged away by mules, and, being mounted, he galloped towards the gun, whereupon the French ran away and Guthrie brought the gun back as a trophy.

After the battle of Talavera, Dr Ferguson, the Deputy Inspector of Hospitals, fell ill with dysentery; Guthrie was again in sole charge, and in the Retreat from Talavera across the Tagus he had to organize the evacuation. The wounded who were evacuated were sent to a hospital established in the Convent of Deleytosa and Guthrie was appalled at the low standard of surgery there, and stepped in to prevent a large number of amputations, stigmatizing the place as a 'slaughter house of the wounded', an action which saved many of the wounded, but did not endear him to the Department.

Later malaria and typhoid fever struck the British and Guthrie himself fell ill and was left behind at Abrantes to die, but survived on self-treatment with two gallons of lemonade a day. He was invalided home in 1810, but recovered quickly, and later that year was promoted Staff Surgeon and returned to Lisbon to join the famous 4th Division in time for the break-out from the lines of Torres Vedras and the pursuit of the French Army of Portugal under Massena. He served at the sieges of Olivença and Badajoz and was the senior surgeon at Albuera where the fusilier brigade lost 1,090 men out of 1,500, and the 57th Regiment (now the Middlesex Regiment) won their nickname of 'Diehards', losing 23 officers and 400 men out of a total strength of 500. Guthrie found himself with 3,000 casualties and only four waggons and the regimental surgical panniers to deal with them, and was working eighteen hours a day for three weeks. Guthrie was so distressed by the poor standard of the general hospitals at the base that after Ciudad Rodrigo he kept the wounded in his regimental hospitals. This again landed him in trouble with the Adjutant General, but he was able to show that the mortality, especially that following amputation, was very much lower in his regimental hospitals than in the general hospitals.

At Salamanca, in addition to caring for the British wounded, Guthrie collected also 300 French wounded and cared for them, browbeating the Spanish authorities into providing facilities by threatening to leave a letter for the French, whom the Spaniards expected to return, telling the General to hang the inhabitants for their inhumanity. The action was repaid a year later when Guthrie himself was captured by French cavalry, commanded by one of those wounded who had been exchanged, and the French officer, recognizing his saviour, immediately released Guthrie. At Salamanca, too, he records a sad but comical incident in connexion with the ricochet shots of cannon balls, saying

'The plunging of shot usually denominated ricochet is a pleasing although awful and deceitful sight, the ball appearing to bound like a cricket ball; and we are only likely to establish its force by the manner which it ploughs up the ground. A poor Irish lad of the 27th Regiment was silly enough to call out to his comrades on seeing a shot of this kind, "Stop it boys"; and to endeavour to do so with his foot, which was smashed to pieces so as to render amputation necessary.'

In 1812 Guthrie was appointed Deputy Inspector of Hospitals and was responsible for the evacuation arrangements on the long retreat back to Portugal, when 2,000 wounded were brought safely back. But his only reward was to hear that the War Office had refused to confirm his promotion, and in spite of strong representations by Wellington he was not promoted until 1813. After service at the base hospitals in Santander, he moved up for the final break through the Pyrenees and was Senior Medical Officer at the Battle of Toulouse in 1814, and the reports of his operative results he records with justifiable pride (Tables 1 and 2).

With Napoleon's exile to Elba, the Army was rapidly reduced in size and Guthrie was placed on half-pay. In 1815 he published his book 'On Gunshot Wounds of the Extremities Requiring Amputation' in which he gave the first serious account of their treatment by one who was really experienced since the days of Wiseman, surgeon to King Charles II. His book is a curious compound of intense practical skill and heroic surgery allied with diligent and compassionate

Table 1

Return of surgical cases treated, and capital operations performed, in the General Hospital at Toulouse, from April 10 to June 28 1814 (Guthrie 1820)

Diseases and state of wounds	Total treated	Died	Discharged to duty	Transferred to Bordeaux	Proportion of deaths to the number treated
Head	95	17	25	53	1 in $5\frac{1}{17}$
Thorax	96	35	14	47	1 in $2\frac{1}{14}$
Abdomen	104	24	21	59	1 in $4\frac{1}{3}$
Superior extremities	304	3	96	205	1 in 101
Inferior ditto	498	21	150	327	1 in $23\frac{1}{7}$
Compound fractures	78	29	-	49	1 in $2\frac{1}{29}$
Gangrene					
Wounds of spine	3	3	-	-	1 in 1
Ditto of joints	16	4	-	12	1 in 4
Amputations:					
Arm	7				
Leg and thigh	41	48	10	38	1 in $5\frac{1}{3}$
Total	1242	146	306	790	1 in $8\frac{1}{148}$

Wounded Officers . . 117, not included.

Among these, 13 cases of tetanus occurred; all proved fatal.

Table 2

Return of surgical cases treated, and capital operations performed, amongst officers at Toulouse, from April 10 to June 28 1814 (Guthrie 1820).

Diseases and state of wounds	Remained	Admitted	Total treated	Discharged	Transferred to Bordeaux	Died	Remaining	Proportion of deaths to the number treated
Head	-	6	6	4	1	-	1	
Thorax	-	10	10	2	2	-	6	
Abdomen	-	1	1	-	-	-	1	
Superior extremities	-	33	33	9	15	-	9	
Inferior	-	49	49	12	21	1	15	1 in 49
Compound fractures	-	7	7	-	1	2	4	1 in $3\frac{1}{2}$
Slight wounds	-	11	11	7	2	-	2	
Gangrene								
Total	-	117	117	34	42	3	38	1 in 40

care for his cases, but bedevilled by the galenic theories of medicine which still survived about inflammation, humours and the calorific.

If we allow for the state of knowledge, especially in the basic sciences, and remember how sanctified and authoritarian was the conception of 'humours', of the 'constitution' as the sole arbiter of infection, how inflammation was regarded as a necessary and vital form of healing, we can discount the curious pharmacological and supportive measures which Guthrie advocates, such as the use of the 'bark' (cinchona), antimony tartrate to encourage vomiting and the free exhibition of calomel, jalap, turpentine and other strong purges. But the practice of bleeding, which he strongly advocates, advising up to 20 oz to be taken off every day for three days in cases of inflammation, may seem to us so harmful and against reason that it is difficult to justify.

However, Guthrie recounts how, in the spring of 1801, when first posted to the 29th Foot Regiment stationed at Torbay and

'exposed to sharp winds from Berry Head many suffered from inflammation of the lungs, some strong, some weak, others old, others young and with variously estimated constitutions. I first treated them as I had been taught in London, but almost all that were attacked, young and old, died'.

He then recounts how he performed post-mortem examinations and found that most had gone on to suppuration; he describes how the officers 'began to be uneasy and it became necessary to meet the difficulty. I made up my mind, that the next case of pleural inflammation should not terminate in suppuration whatever else might be the result, instead, then, of attending to the pulse and to the question of blood drained, I only considered the general capacity of my patient and, knowing his constitution to be good, I bled him until an obvious effect was produced, and until the breathing became free, and the pain was nearly or entirely removed. This man rapidly recovered; so did others to my satisfaction; indeed since that period, I have hardly ever lost a case that I have seen in proper time. I had found the clue I wanted to move me from the labyrinth in which I was involved; and it was a leading incident in my life. I gained the approbation of a body of men, who were for a moment doubtful, but who, after the lapse of twenty years, bestowed upon me as a public mark of their esteem and acknowledgment of services rendered as surgeon of their Regiment, the most valuable present that has yet been offered to any officer of that rank.'

He then goes on to describe how the same practice had been successful in the treatment of enteritis cases and in a case of hepatitis. So it is easy to see how he was misled into believing that this

bleeding, which undoubtedly relieved the incipient right heart failure of his pneumonia cases, was a universal panacea.

When we turn from the general treatment of the wounded to the local care of the wound, we perceive Guthrie's greatness. He exploded many of the time-honoured errors of treatment and revolutionized traumatic surgery. He condemned the use of the tourniquet, saying that the advocacy of its use had arisen from generalizing too much 'when the authors had not been actors in the scenes they described' and goes on to say

'Hence I have seen a surgeon on the field of battle, groaning under the weight and inconvenience of a sack full of tourniquets, not one of which he would in all probability, have a proper opportunity of applying, and tormenting himself for days after the action, in the expectation of secondary haemorrhages, which never take place.'

He even discarded its use in amputation, describing how easily the vessels could be picked up between finger and thumb and ligated. He was the first to show that both ends of a divided artery must be tied and that secondary haemorrhage under this regime was very rare at less than 8 per 1,000 cases. He described gas gangrene minutely and stressed the need for avoiding tension to prevent this, emphasizing incision of the deep fascia and describing how tight sutures and the use of compressive bandaging contributed to this eventuality. But he poured scorn on Larrey's theories, saying

'He considers this humid or traumatic gangrene as a deleterious principle, which is capable of spreading by infection or contagion, and is consequently irresistible whilst he supposes, on the contrary, that the gangrene which arises from cold, becomes a stimulant and induces the vessels to act in order to separate the dead from the living; an hypothesis which is entirely imaginary, supported by no known principles, and invented apparently to account for a difference which he could not otherwise explain.'

He described the treatment of nerve injuries, stressing the danger of ligating the ends of nerves and describing the end bulb and its association with causalgia; here, as always, his case reports contain delightful personal touches and he describes how an officer with a brachial plexus lesion and a wounded knee-joint recovered after amputation of the leg but the arm remained paralysed. He gives the follow up, saying

'Fourteen years have now elapsed, and he has now grown stout, is in excellent health but the arm remains nearly the same. He has also been indicted for a rape; but the magistrates, very properly, however they might admit the attempt, would not consent to the admission of the fact.'

He also was the first, incredible as it may seem,

to insist that in fractures of the femur, the leg be aligned as nearly straight as possible. Previously these fractures were always treated in external rotation in the position in which they were found.

It was in advocating early surgery and especially early amputation of dead or disorganized limbs and those with combined vascular, nerve, and bone injury, that Guthrie so advanced the practice of surgery. He placed the normal amputations on a sound anatomical footing, deriding ligature of the artery at a distance from the site of the operation and giving the operative details clearly and fully; but his great success was in showing that amputation through the hip-joint and amputation of the shoulder-joint were safe and practicable procedures. As he says in the preface of the second edition of his work:

'The time of the Peninsular War led to another important result in surgery; it dissipated the illusion which had so long obtained possession of the minds of surgeons of every description that it was impossible to command the flow of blood through the great arteries. I overturned at once this hypothesis, declared it to be visionary and not only without foundation, but with reverse of fact. On the return of the medical officers of the Army to London in 1814, it was not a little amusing to them to hear teachers of surgery gravely informing their students, that amputation at the shoulder-joint was a most formidable operation, on account of the impossibility of effectively preventing the flow of blood through the arteries; and when they did notice amputation of the hip-joint it was only to declare it a murderous operation.'

But this is not to say he was an indiscriminate amputator, and he resolutely condemns amputation when more conservative measures would be successful, and especially in the upper limb he stresses the need to preserve viable tissues and describes the operation of excision of the head of the humerus in gunshot wound of the shoulder giving in great detail the functional results to be expected.

In 1815 when Napoleon returned from Elba for 'The Hundred Days', Guthrie offered to return to active service, but there was the inevitable

bickering about his rank and conditions of service so he posted over to Belgium at his own expense and was in time to operate on some of the Waterloo casualties where again his case notes are a delight to read. The War Office refused to recognize his return to service as official, and the episode cost Guthrie £40. It was perhaps this still ranking that made Guthrie refuse a knighthood offered to him by the Duke of York in 1826, on the grounds that he was too poor.

This concludes my short account of Guthrie, the Peninsular Surgeon, but, although he was the recognized exponent of military surgery, and feted in Paris when he lectured there, he was only 30 years of age when he came to the end of this eventful career which was but a prelude to his eminence in surgery. He became an acknowledged master of ophthalmic surgery as well as general surgery. In 1823 he was made Assistant Surgeon at the Westminster Hospital and in 1824 a member of the Council of the Royal College of Surgeons. In 1826 he became Surgeon at the Westminster Hospital and a Fellow of the Royal Society; he was Professor of Anatomy at the Royal College of Surgeons in 1828. He was on the Court of Examiners and Vice President in 1831; President of the Royal College of Surgeons, in 1833, 1834, 1841 and 1854; and one of the original three hundred fellows. He died on his birthday in 1856 after fifteen years in the service of the King, and fifty-eight years in the service of humanity.

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Section of Experimental Medicine and Therapeutics

President A C Dornhorst MD

Meeting March 14 1961

Papers

Intestinal Absorption

by Professor D H Smyth MD (Sheffield)

A good deal of progress in the investigation of intestinal absorption in the last decade has depended on the use of *in vitro* techniques, introduced by Fisher & Parsons (1949). By *in vitro* techniques in absorption, we mean the use of segments of intestine completely deprived of their normal blood supply. At first sight these preparations seem highly unphysiological, and some of them even absurdly so, but in spite of this they have shown their value, and have provided a great stimulus to the physiology of intestinal absorption. One of the most useful, and apparently one of the least physiological, is the everted sac of small intestine, which was developed in the Physiology Department in Sheffield by Wilson & Wiseman (1954). It is being extensively used in this country and America at present and offers a very simple experimental approach to problems of absorption. A rat is anaesthetized, and the intestine quickly removed by pulling it away from the mesentery. The intestine is then everted on a glass rod. The everted intestine is now divided into segments of various sizes and from these sacs are made. The sacs are filled with physiological saline, suspended in physiological saline in conical flasks and shaken for 30 minutes, one hour or longer. At the end of the experiment the fluid in which the sac is shaken can be measured and analysed, and also the fluid inside the sac and in the intestinal wall, and in this way it can be shown that substances are taken up by the epithelial cells and are transferred to the inside of the sac. The first question that might be asked is what is the relation of this process to physiological absorption, as in physiological absorption the substances absorbed do not pass through the muscle layer of the intestine. Substances absorbed from the lumen of the intestine are taken up by the epithelial cells and transferred to the other side of the cell, where they enter the subepithelial space. Under physiological conditions they pass into the

blood and lymph vessels, and are removed by these channels. Under *in vitro* conditions part of the fluid remains in the subepithelial space, but part passes through the muscle layer. This passage is in fact partly by the physiological route through the cut blood and lymph vessels and this is shown by the fact that the first fluid that comes through is blood stained. A certain amount of fluid remains in the subepithelial space. What we obtain inside the sac is therefore not quite so unphysiological as appears at first sight.

In the last six years we have done a great many experiments of this kind and we have taken care to control these with experiments with various types of *in vivo* preparations, i.e. where the intestine has its normal blood supply. The *in vitro* intestine undoubtedly carries out very similar activities to those which occur *in vivo*, and furthermore it does so in a way which makes it far more amenable to experimental investigation.

The general result of work of this kind is to suggest that the mechanism of transport of many substances is much more complex than once seemed likely, and often involves active participation by the intestinal cells. Absorption is, in fact, often an active process. There are various ways of defining what is meant by an active process, but here I would take the definition that the forces for absorption are created by the epithelial cells, the energy being obtained from their metabolic activity. The meaning of this can be appreciated by considering an example. If a substance is taken into the alimentary tract and digested, a concentration of various products is produced in the lumen of the intestine, and this concentration may be sufficient to enable diffusion to take place across the intestinal epithelium. In this case the force necessary for diffusion is produced by the high concentration, and is not created by the epithelial cells themselves. If, however, a substance is present in the lumen of the intestine in smaller concentration than in the blood, then energy must be provided by the epithelial cells for movement and in this sense the

process is active. We have now clear evidence that active processes of this kind involve at least some of the products of digestion of proteins, fats and carbohydrates, and also fluid and some inorganic salts, and a variety of mechanisms exist in the epithelial cells for causing movement of these substances.

But the *in vitro* preparation enables us to go further than simply say whether the epithelial cells participate in active transport. We are now beginning to analyse the processes involved, and although not much progress has been made, in some cases we know that at least several stages take place in the mechanism and we have also some idea about the localization of these in the cells and their relation to cellular metabolism. I believe that advances in the physiology of absorption are going to be made chiefly in this direction, i.e. separation of the various stages in movement and relation of these to definite parts of the cell, definite structures in the cell, or definite enzyme systems in the cells. I shall illustrate some of these points by reference to the absorption of protein and glucose.

Protein

The classical view of protein absorption is that digestion of amino acids occurs in the intestine and the amino acids are then absorbed. This view was challenged by Fisher (1954) who suggested that aggregates larger than amino acids might be absorbed and possibly even whole proteins. We undertook a series of investigations to attempt to clarify this problem, but we very soon realized that the question we were trying to answer was not adequately framed. There were in fact not one question but two questions. The first was the form in which protein leaves the lumen of the alimentary tract, and the second the form in which it enters the blood stream. The answers to both these questions are now quite definite. Protein can leave the alimentary tract in products larger than amino acids, but the protein enters the blood stream almost exclusively in the form of amino acids. (I refer here to the amounts of protein related to nutritional quantities, because it is quite certain that very small amounts of whole proteins can pass through the intestinal barrier.) In coming to these conclusions we have used both *in vivo* and *in vitro* techniques, but I will choose the *in vitro* as an illustration. An everted sac is shaken for 30 minutes in a solution containing a peptide, and at the end of this time, a sample of the fluid is taken for analysis; the wall of the intestine and the fluid inside the sac are also analysed. A certain amount of amino acid is formed. This might be explained by hydrolysis by peptidases in the luminal fluid (i.e. the fluid in which the sacs are shaken), or it might be by

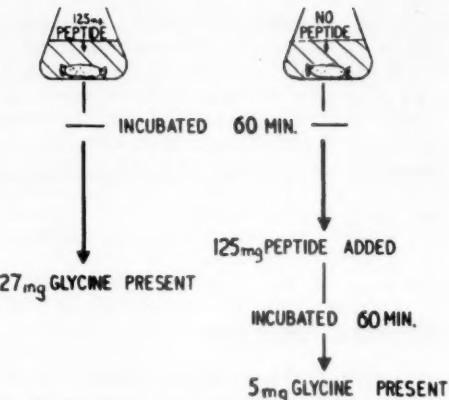


Fig 1 Experiment showing that most of hydrolysis of glycyl-glycine must take place after it has entered the mucosal cell, and not by peptidases in the fluid in which sacs are suspended

hydrolysis inside the intestine after peptide has entered the cells. We can easily distinguish between these by incubating peptide in the luminal fluid (Fig 1), without the presence of the sac, and this shows clearly that the luminal fluid peptidases could only account for a small amount of the total peptide hydrolysed (Newey & Smyth 1960). There seems little doubt therefore that peptide must enter the epithelial cells as such and undergo intracellular hydrolysis. What we understand by protein digestion may therefore take place not only in the lumen of the intestine but also intracellularly. This was in fact guessed at by many of the older workers but not explicitly demonstrated.

One of the arguments about the form of protein absorption is the rate at which digestion occurs, as it has been suggested that breakdown to amino acids could not take place at a sufficiently rapid rate. Our experiments show that luminal breakdown to amino acids is not essential in order that amino acids should enter the blood stream. Crane & Neuberger (1960) have recently published results suggesting that protein digestion may in fact be very rapid, as the difference in time of appearance of amino acids in the blood stream after giving a protein hydrolysate and the unhydrolysed protein may be as little as 15 minutes.

At present we are trying to find out more about the intracellular mechanisms for transport of protein and amino acids. If we carry out experiments with amino acids it can be shown that a number of amino acids are transferred by the intestine against a concentration gradient (Wiseman 1953, 1955). There is also competition between different amino acids, and methionine can compete effectively with most other amino acids for the mechanism. In trying to localize such

a mechanism one approach is to ask whether the mechanism is located at the entrance to the cell, or whether it is an exit mechanism dealing with amino acids which have entered by diffusion. We can use the intracellular hydrolysis of peptide as a method of getting amino acids into the cell, without the amino acid, as such, having to enter the cell. We can also, however, use it to study entry of peptide as distinct from entry of amino acids, and by experiments of this kind we can get some information about the localization of mechanisms inside the cell.

The following are some preliminary conclusions we have reached: Peptides enter the cells mainly by diffusion but not entirely so, because the amount of peptide entering is reduced by anaerobic conditions. Since, however, this reduces water absorption it is possible that peptide entry depends partly on solvent drag, i.e. the peptide is transported in an active water stream. Once the amino acid is formed inside the cell it may either diffuse back into the lumen of the intestine or it may be transferred across the cell to the subepithelial space, and by studying various conditions we can find effects which modify these two processes. The most important condition affecting this process is anoxia, and in this condition most of the amino acid diffuses back instead of being transferred forward.

Our concept of peptide and amino acid transfer is thus as follows: Peptides may enter the cell as such, and amino acids are formed by intracellular hydrolysis. Part of the amino acid formed attaches itself to a carrier in the cell, and part diffuses back again out into the lumen (Fig 2). This carrier requires the presence of aerobic energy and in anaerobic conditions or in the presence of DNP most of the amino acid formed inside the cell diffuses back into the lumen. There is thus a carrier mechanism inside the cell as distinct from a carrier mechanism at the luminal border of the cell. Amino acids in the lumen of the intestine may use the same carrier mechanism, but there is certainly another mechanism involved, i.e. at entry

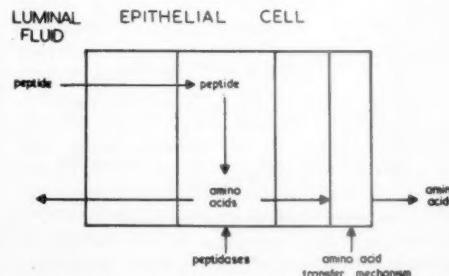


Fig 2 Fate of amino acids formed by intracellular peptidase activity

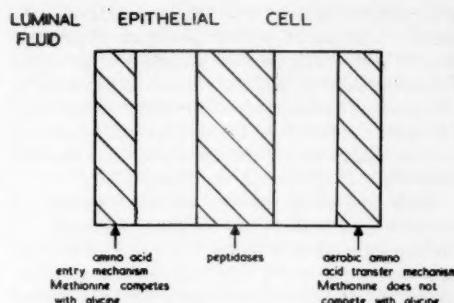


Fig 3 Possible intracellular location of various processes involved in peptide hydrolysis and amino acid transfer

into the cell. This can be shown by the study of competition between amino acids (Newey & Smyth 1961). Methionine inhibits the entry of glycine into the cell but it inhibits much less the exit of glycine formed intracellularly. There are thus two stages in glycine transfer, an entry mechanism and an exit mechanism. The entry mechanism is where competition with methionine occurs, the exit mechanism does not involve methionine competition but requires aerobic energy (Fig 3). Another interesting possibility is that these two mechanisms may have different specificities for different amino acids, and this may explain some of the curious results which have been obtained in relation to the specificity of amino acid transfer.

Glucose

The question of glucose transfer has attracted great interest for a long time and has been very well reviewed by Crane (1960). The first question that arises in this connexion is the status of the phosphorylation theory. According to this theory glucose is phosphorylated at the mucosal border of the cell, is carried across the cell as a phosphorylated compound and is subsequently dephosphorylated. Since first put forward by Wilbrandt & Laszt (1933), this theory has persisted and still keeps its place in many modern textbooks. It is not widely appreciated that those who put it forward soon withdrew their support; there is no real evidence in favour of the phosphorylation theory and there is a good deal of evidence against it. In fairness to the authors of the theory, it should be stated that it was put forward at a time when the part played by phosphorylating reactions in metabolism was not so widely known as it is now, and it was not recognized that substances which interfere with phosphorylation might produce effects by interfering with metabolism. There are two major types of evidence against the phos-

phorylation theory: (1) Many sugars can be actively transported which cannot be phosphorylated. (2) By using labelled glucose and galactose it has been shown that the glucose transported by the intestine has not passed through the glucose-6-phosphate pool. These are very serious objections to the phosphorylation theory of glucose absorption (for references see Crane 1960).

What in fact do we now know about glucose transfer, and is there any modern alternative to the phosphorylation theory? No precise scheme has been put forward to explain glucose transfer, simply because no precise scheme has yet been put forward which adequately explains transfer of any substances across biological membranes. Modern views tend to think of carrier mechanisms, the carrier being probably of a protein nature, and it would seem likely that the transfer of glucose by the intestine involves a carrier mechanism of this kind. The following facts are well established: (1) Glucose can be moved against a concentration gradient. (2) The movement of glucose depends on aerobic energy and does not happen in anaerobic conditions. (3) It shares a mechanism with at least some other sugars, e.g. galactose. (4) It is inhibited specifically by phlorrhizin. It is also inhibited by a great many other substances, but none of these have the specificity of phlorrhizin, nor do they act in anything like as small a concentration. Phlorrhizin is able to affect glucose transfer in a concentration as low as 10^{-6} M.

The action of phlorrhizin has given some interesting clues as to the nature of the mechanism for glucose transfer (Newey *et al.* 1959). For example it is possible to study the effect of phlorrhizin on the entry of glucose into the cell as distinct from its transfer. This can be done by using ^{14}C -labelled glucose and collecting from the intestine the metabolic CO_2 (Fig 4). If the CO_2 is labelled it is a reasonable conclusion that the

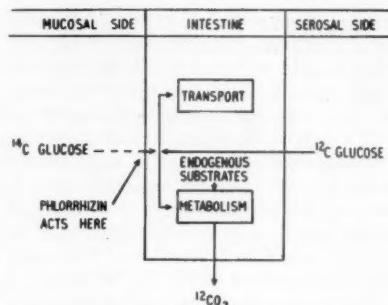


Fig 5 Site of action of phlorrhizin in inhibiting intestinal transfer of glucose

labelled glucose must have entered the cell. If experiments are done in which labelled glucose is present on either the mucosal or the serosal side of the cell it can be shown that phlorrhizin will affect the amount of labelled CO_2 formed, and two different effects are produced. If we have a high concentration of phlorrhizin (10^{-3} M) we find that production of CO_2 from glucose on either side of the intestine is greatly reduced, and this suggests that phlorrhizin acts on the metabolism of glucose inside the cell. If, however, we use a much smaller concentration of phlorrhizin, we can show that the effect of phlorrhizin is to prevent metabolism of glucose initially present on the luminal side of the intestine but not on the other side (Fig 5). There must therefore be an entry mechanism which is inhibited by phlorrhizin. We can get some further information about the mechanism of glucose transfer by comparing the effects of phlorrhizin, anaerobic conditions and 2:4-dinitrophenol (DNP) on glucose transfer. All these abolish the active movement of glucose by the intestine. In contrast to this, anaerobic conditions and DNP do not prevent the entry of glucose into the cells and from this it follows that there are at least two stages in the transfer of mechanism of glucose: (1) An entry mechanism

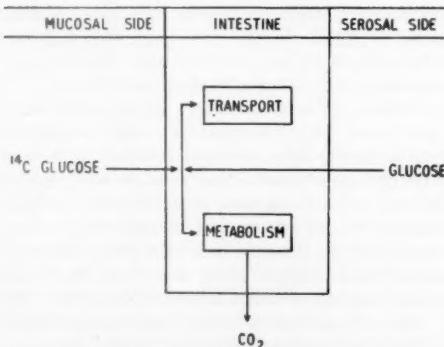


Fig 4 Fate of glucose initially present on either mucosal or serosal side of the intestine

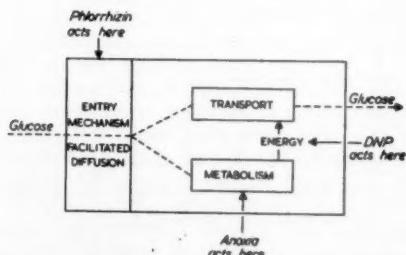


Fig 6 Possible location of mechanisms involved in intestinal transfer of glucose

which is inhibited by phlorrhizin. (2) A mechanism which is prevented by anaerobic conditions (Matthews & Smyth 1960). It seems possible that this second mechanism is the one responsible for movement against a concentration gradient. Hence it seems likely that, as in the case of amino acids, the transfer by the intestine is a complex process and involves more than one stage. A scheme showing the possible sites of action of different inhibiting conditions is given in Fig 6. In this it is suggested that the phlorrhizin sensitive entry mechanism may be a facilitated diffusion. This is an interesting speculation but has not yet been proved.

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Motility of the Intestine

by Edith Bülbbring MD MA FRS (*Oxford*)

It is known that peristaltic activity is entirely under nervous control, but a few years ago we were able to throw some light on the mechanism of the reflex and on its intrinsic nervous pathway (Bülbbring, Lin & Schofield 1958). We obtained evidence that the sensory receptors, which trigger the reflex when the intestine is extended and the filling pressure rises, are situated in the deepest layers or at the base of the mucosal epithelium. The sensory fibres arise mainly from cells in the submucous plexus of Meissner which contains a large number of unipolar or bipolar neurons. Their axons make connexions with multipolar ganglion cells chiefly situated in the myenteric plexus of Auerbach. The submucous plexus appears therefore to be mainly sensory, while the myenteric plexus contains mainly the motor neurons innervating the muscle.

The peristaltic reflex was found to depend on the integrity of the mucosa. If the mucosa was removed, or asphyxiated, or a local anaesthetic was applied to its surface the peristaltic reflex was abolished. More recent experiments by Ginzel (1959) suggest that some sensory receptors might be slightly further removed from the mucosal epithelium, possibly in the muscularis mucosae. Whatever their exact site, they are situated in close proximity to the enterochromaffin cells which are

also found in the deep layers of the mucosa. The release of 5-hydroxytryptamine (5-HT) from these cells exerts an important subsidiary action on peristalsis. 5-HT is a sensory stimulant and it is known to excite sensory endings in many parts of the body. In the intestine, where it is locally produced and released in proportion to the rise of intraluminal pressure, 5-HT lowers the threshold of excitation of the mucosal nerve endings and thereby has a modulating influence on peristalsis (Bülbbring & Lin 1958, Bülbbring & Crema 1958, 1959).

The peristaltic contractions are produced by the concerted activity of an immense number of very small muscle cells whose properties we are only just beginning to understand. They are very thin and not very long, measuring about 5 μ by 100 μ . It is fascinating to think that these cells are really like a large population of independent beings, like a crowd of unicellular organisms, rather primitive, not so highly specialized as for example skeletal muscle, and capable of several functions, all united in one and the same cell. This cell can be the focus of excitation or it can be excited by a stimulus from elsewhere. It can also behave like a sensory receptor and, in addition, it can contract. Moreover, the intestinal smooth muscle contracts not only in response to a nervous impulse, but it can contract spontaneously, and it does so, rhythmically, like the heart.

Like the heart, intestinal smooth muscle has an intrinsic rhythm, it generates action potentials and each action potential is followed by a small individual contraction. Unlike the heart, these contractions can summate and this is the basis of what is generally known as 'tone' (Bozler 1948, Bülbbring 1957). Spontaneous changes in tone are commonly observed and they are entirely the consequence of spontaneous changes in the frequency at which action potentials are discharged. If the frequency is high the individual contractions may fuse, like a tetanus, to a high maintained tone. If the discharge rate is low there is time for relaxation before the next impulse arises and the muscle tone declines.

One peculiar property of intestinal smooth muscle is that the more it is stretched the higher its tone. It endeavours to contract against the extending force. The stimulus is stretch, and the response is the same as the response of a stretch receptor, i.e. a burst of impulses or, if rhythmic discharge was already present, an increased rate of firing. Stretch deformation of the cells leads to a depolarization of the membrane which in turn leads to the firing of impulses. The cell produces the typical response of a sensory organ to its specific stimulus. However, the intestinal smooth muscle cell is not a specific receptor. To every

kind of stimulus, be it mechanical, electrical or chemical (e.g. acetylcholine or histamine), it reacts with a change of spike frequency (Bülbbring 1955). The stronger the stimulus, the higher the rate of rhythmic discharge and consequently the contraction. There is a perfect correlation between the rate of spike discharge and the development of tension. This is found regardless of whether the electrical activity is recorded from a large number of cells by surface electrodes or by an intracellular electrode from one single cell.

The mechanism for integrating individual activities to produce a synchronized contraction is very efficient and it is due to the fact that transmission of excitation takes place from cell to cell (Bülbbring, Burnstock & Holman 1958). The pacemaker for spontaneous rhythmic activity is not located at a constant site as it is in the heart. On the contrary, every cell is a potential pacemaker and this function shifts from cell to cell, now here, now there, each cell being able to drive its neighbour or to be driven by an adjacent cell. Thus, though the rate of the spontaneous discharge is often very regular, the individual spikes may differ considerably in shape and frequently represent a mixture of locally initiated and propagated action potentials. Excitability fluctuates partly as a result of the tendency of every cell to fire its own spontaneous rhythm, partly as a result of slow overall fluctuations in the membrane potential the origin of which is as yet unknown.

Recent observations have thrown some light on the mechanisms which determine the membrane potential and influence excitability of the intestinal muscle. Firstly, Goodford & Hermansen (1960) observed that the muscle is extremely permeable to sodium. Using radioactive tracers, they found that sodium exchanges at a rate which is 50–100 times faster than that of potassium; 90% of the total sodium exchanges with the outside within a minute. With such an astonishing membrane permeability to sodium, active extrusion of sodium must be of the greatest importance in maintaining a concentration difference between the inside and outside of the cell. Active cation transport requires energy, and normally, in this constantly active tissue, the cell appears to be rarely in a condition in which it can reach its resting potential. If the rate of energy supply is increased, however, a stable membrane condition can be attained, as was shown in recent experiments in which we measured biochemical and biophysical phenomena simultaneously and studied in particular the action of adrenaline.

Adrenaline inhibits intestinal smooth muscle. It stops the spontaneous activity, the tissue becomes electrically inexcitable, and the membrane potential increases. The muscle relaxes

because the action potentials stop. In one muscle strip we measured these phenomena. In parallel strips of muscle, taken from the same animal and exposed to identical conditions, we measured phosphorylase activity. And we found, in every experiment, that simultaneously with the inhibitory effect of adrenaline there was an increase in phosphorylase activity (Axelsson *et al.* 1959). This enzyme accelerates the breakdown of glycogen. Our experimental results suggest that the stimulation of one reaction in a chain of biochemical processes might make more metabolic energy available for active mechanisms concerned with the stabilization of the membrane. Therefore, in this very unstable tissue, adrenaline leads to relaxation.

It is known that adrenaline has this inhibitory effect only in some smooth muscles, and that it acts in the opposite way on others, causing a contraction. Presumably adrenaline has a dual action: one on the membrane directly, causing excitation; the other on carbohydrate metabolism, affecting metabolic rate and thereby in certain tissues causing inhibition. Which of the two actions predominates depends on the state of the cell (Bülbbring 1960). Adrenaline causes a contraction generally in those smooth muscles which are normally activated by their nerves. In the absence of nervous stimulation, they are quiescent, and their membrane potential is presumably stable. An increased supply of metabolic energy cannot make it more stable than it already is and thus adrenaline only exerts its stimulating action. But in the intestine the metabolic action of adrenaline predominates and activity is stopped. The increased supply of metabolic energy accelerates the active cation transport. This can be shown with radioactive tracers. During the inhibition by adrenaline the rate of uptake of potassium into the cell and the rate at which sodium is extruded are both increased.

The hypothesis can be tested in various other ways. For example, we exposed the tissue to a glucose-free medium in an attempt to deplete it of glycogen in order to see whether the action of adrenaline would be modified if there was no substrate for phosphorylase available. The first effect which is observed when the external source of energy is removed, is that the tissue relaxes. It relaxes, however, not because the action potentials stop. On the contrary they are discharged at a faster rate, but they now fail to produce a contraction. The restoration of glucose to the medium has two effects. It restores the contraction and it stabilizes the membrane. Thus, while removal of glucose increases membrane activity, the restoration of glucose to the medium stops it (Axelsson & Bülbbring 1960a).

Obviously, the available energy is distributed into two channels. It is utilized (1) for the contractile mechanism, and (2) for the stabilization of the membrane. Adrenaline, in the early stages of glucose depletion has the same effect as the restoration of the exogenous glucose. Only, adrenaline achieves its action by making energy available from endogenous sources (Axelsson & Bülbring 1960b).

After glucose depletion has proceeded to such an extent that the glycogen store is depleted, adrenaline has a stimulant action. It depolarizes and causes the discharge of spikes. The inhibitory effect is also converted into a stimulant effect in the presence of iodoacetate, a metabolic inhibitor.

Another simple way of increasing metabolic rate is to raise the temperature. We observed an effect analogous to that of adrenaline if the temperature was quickly raised, e.g. from 27° to 37°C. This produces in the intestinal muscle a transient cessation of spike activity, muscular relaxation and hyperpolarization of the membrane. Conversely, if the temperature is suddenly lowered over this range, activity is accelerated.

It is clear that in rhythmically active smooth muscle of the intestine the rate of metabolic energy supply is an important factor influencing membrane potential and excitability. The tissue which is continuously in a condition of excitation requires a very active mechanism for keeping up the differences in ionic concentration. The tendency to depolarize (due to the peculiar properties of the membrane, particularly its high sodium permeability) is constantly opposed by forces which try to stabilize the membrane. It may be that sodium occupies a key position, in that normally the changes of the intracellular sodium concentration which influence the rate of sodium extrusion are also coupled to the rate of metabolic energy supply.

It is too early to attempt an interpretation of clinical observations by results obtained on a cellular level. This connexion will have to be developed by future work.

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Clinical Implications of Recent Advances in the Physiology of Motility and Absorption

by E N Rowlands MD FRCP (London)

Those engaged in clinical research in gastroenterology have long been acutely aware of the urgent need for experimental work at the cellular level, and the new techniques are in many ways more physiological than many of the bizarre surgical procedures which have dominated gastrointestinal physiology in the past. For example, the traditional methods of the experimental physiologist have continued to obscure rather than clarify the physiology of the intestinal movements since Bayliss & Starling remarked in 1899 that there were more 'discrepancies of fact and opinion' in this branch of physiology than in any other. The response of intestinal smooth muscle to stimulation was capricious and unpredictable. Sir Henry Dale (1957) stated that the fundamental problem was that 'different tracts of apparently similar involuntary muscle give opposite responses, not only to impulses in nerves with the same anatomical connexion, but also to the artificial application of one and the same chemical transmitter of the effects of such impulses'. Yet this problem has now been largely resolved by the development of *in vitro* techniques for recording simultaneously the functional, biophysical and biochemical changes in a single smooth muscle cell.

In this way, Dr Bülbring has shown that adrenaline, for example, has two actions which are often antagonistic, one on the cell membrane and the other on the metabolism of the cell; and it is now possible to understand how adrenaline may cause either contraction or relaxation of a muscle. From the clinical standpoint it is interesting to speculate whether smooth muscle cells may suffer from some biophysical or biochemical disorder which renders them resistant to a transmitter such as adrenaline. Such a disorder might explain the mysterious clinical problem of why the cardiac sphincter fails to relax in achalasia or cardiospasm. In this disease the body of the oesophagus is completely denervated and therefore incapable of conducting peristaltic waves. The cholinergic innervation of the cardiac sphincter on the other hand is intact (Ellis, Kauntze, Nightingale & Trounce 1960), but the sphincter is not in a state of spasm, and although it does not relax reflexly on swallowing it contracts in the normal manner at the end of the act of swallowing (Edwards & Rowlands 1959). The only drugs which will relax the sphincter are the nitrates which act directly on smooth muscle. Since the circular muscle of the cardiac

sphincter in normal persons appears to respond to nervous stimulation by relaxation (Ellis, Kauntze & Trounce 1960) it seems that either the muscle cells of the sphincter are refractory in achalasia or that insufficient transmitter substance is released. Presumably this difficult clinical problem could be resolved by applying Dr. Bülbbring's techniques to strips of the cardiac sphincter removed at operation.

Although Dr Bülbbring's work has clarified the behaviour of the individual smooth muscle cell, it is difficult for the clinician to visualize how the activity of the muscle cell links up with the intramural nerve plexuses, not to mention the extrinsic nerves. The fluctuations of intraluminal pressure in the human intestine, as measured with open tubes or radio pills, produce a spontaneous basic rhythm. The frequency of this rhythmic pattern varies at different levels in the intestine but is remarkably constant at any one level, falling from 11 per minute in the duodenum and jejunum, to about 8 per minute in the terminal ileum and about 2 per minute in the colon. The precise meaning of these intraluminal pressures is not at all clear and their relationship to the tone or tension of the intestinal wall is obscure (Edwards & Rowlands 1960). It is therefore tempting to equate these pressures with the spontaneous rhythmic activity of the individual smooth muscle cells in Dr Bülbbring's preparations, each cell being its own pacemaker. However, it seems much more likely that the resting rhythmical pressures in the human intestine reflect the activity of the muscle wall as it is influenced by the intramural nerve plexuses, and I think it would be premature to discard the useful concept of a pacemaking area in the duodenum (Milton & Smith 1956). It is much easier to understand the peristaltic activity of the human intestine in terms of Dr Bülbbring's work, because it involves an intrinsic nervous pathway which is triggered by a rise in intraluminal pressure. Hence, the sudden distension of the lumen by a bolus of food, for example in the oesophagus or duodenum, stimulates peristalsis and rapid transit through these areas, in contrast to other areas such as the colon.

Very little is known about the effect of motility on absorption and it is therefore difficult to link together the recent physiological advances in these separate fields of study. The biochemical activities of smooth muscle cells are adversely affected by loss of potassium and therefore this is an important factor in the pathogenesis of ileus. Again, malabsorption often occurs in patients with systemic sclerosis, presumably because of the gradual disappearance of the smooth muscle cells so that the intestinal loops become distended and immobile.

However, it is much more difficult to determine whether defective motility is an important factor in causing intestinal malabsorption in celiac disease and other forms of steatorrhoea.

The techniques available for studying the problem are so inadequate that very little is known about the relation between motility and absorption even in normal subjects. Neither intestinal tone nor the rate of transit of food can be measured accurately in the human intestine. Nor is it always possible to distinguish between peristaltic activity, which tends to reduce the period of contact between the absorbable material and the mucosa, and segmental activity which favours absorption (for example of water from the colon). There is some experimental evidence that drug-induced hypermotility increases the absorption of glucose and methionine in normal subjects (Cummins & Almy 1953), and that hypomotility induced by propantheline reduces the rate of sodium absorption, but the correlation between the amount absorbed and the amount of motor activity was not impressive (Grosier & Farrar 1960). However, it seems likely that current studies using radio-pills and other modern techniques to record motility, will show that defective motility plays some part in reducing the absorption of a wide variety of substances in gluten-induced celiac disease. An interesting and important link between motility and absorption in this disease is the recent observation by Schneider *et al.* (1960) that certain fractions of gluten will inhibit the peristaltic reflex when applied to the serosa of isolated loops of the jejunum of rats. This inhibitory effect does not occur if the gluten fraction is instilled into the lumen or if it is incubated with normal mucosa before being applied to the serosa. The gluten fractions probably act by decreasing the release of acetylcholine (Schneider & Bishop 1960).

The demonstration that gluten has this 'toxic' effect on peristalsis perhaps strengthens the view that in patients with celiac disease it may also be 'toxic' to those enzymes in the mucous membrane which play an essential part in intestinal absorption. This has always seemed probable but there is no direct evidence for it. On the other hand, there are several cogent objections to the view that the malabsorption in this disease can be attributed entirely to atrophy of the villi and the consequent reduction in the total absorbing surface. Thus the delayed absorption of protein, which was recently demonstrated so elegantly by Crane & Neuberger (1960) using the stable isotope ^{15}N , may be partly a consequence of the toxic effect of gluten on peptidases in the mucous membrane. This would fit in with Professor Smyth's observation that protein passes into the luminal cells mainly in the form of peptides which

then undergo intracellular hydrolysis. Similarly the process of fat absorption involves re-esterification of long-chain fatty acids within the mucosal cells, and Dawson & Isselbacher (1960) have recently shown that homogenates of jejunal mucosa from patients with idiopathic steatorrhoea have a greatly diminished capacity to esterify these fatty acids. Although this may be partly explained by the reduction in the total number of mucosal cells in this disease, it is possible that gluten may be 'toxic' to some of the co-factors which are necessary for esterification. Moreover, Milne *et al.* (1960) have recently shown that in some rare metabolic disorders there is impaired transport by the jejunal cells of certain specific amino acids. Thus the absorption of L-tryptophan was delayed and incomplete in Hartnup disease, and the transport of lysine and ornithine by the jejunal cells was grossly impaired in homozygous cases of cystinuria (Milne *et al.* 1961). Milne and his colleagues also obtained suggestive evidence of delayed absorption of D-tryptophan in Hartnup disease, and this provides further evidence in favour of Professor Smyth's view that the absorption of D-amino acids also involves an active biological process.

Dr Bülbring, in her studies on the relation between 5-hydroxytryptamine and motility, observed that peristalsis was stimulated when 5-HT was introduced into the lumen of the isolated guinea-pig ileum because it lowered the threshold of excitation of the sensory receptors in the mucosa so that the peristaltic reflex was elicited at a lower intraluminal pressure. In man, however, the instillation of 5-HT into the jejunum had no effect on intestinal motility as recorded by a balloon (Hendrix *et al.* 1957). Nor did the ingestion of large amounts of 5-HT in the form of bananas cause diarrhoea or any other abdominal symptoms in a group of normal subjects, although their urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) was elevated into the range which is commonly regarded as diagnostic of carcinoid tumours (Connell *et al.* 1960). It may well be that species differences are important because Dr Bülbring found that the effect of 5-HT was much more obvious in the guinea-pig than in the rabbit, whereas the administration of 5-HT by mouth to mice is said to have the same effect as large doses of senna (Collier 1958). However, it seemed possible that overproduction of 5-HT might occur in some patients, for example those with chronic simple diarrhoea of unknown aetiology, but we found that the excretion of 5-HIAA was within normal limits in this disease and also in patients with steatorrhoea. Kowlessar *et al.* (1958), however, found that the urinary 5-HIAA was slightly elevated in patients with 'symptomatic non-

tropical sprue' but it returned to normal levels when the symptoms had been controlled by a gluten-free diet. We cannot explain the discrepancy between their findings and ours but it is difficult to understand why there should be an overproduction of 5-HT if it is true that the motility of the intestine is depressed in this disease. Thus Dr Bülbring found that active peristalsis released 5-HT from the mucosal epithelium in proportion to the rise in intraluminal pressure, and it has also been reported that in man the 5-HT level in the blood rises when peristalsis is stimulated with mecholyl or magnesium sulphate (Adams 1960). Thus it appears that 5-HT is liberated in association with increased intestinal activity.

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Meeting May 9 1961

Professor A C Dornhorst delivered his Presidential Address on **Circulatory Dynamics**

Meeting July 21 1961

The meeting took the form of a Public Report Session following the Ciba Foundation Symposium on **Pulmonary Structure and Function**. Dr Dickinson W Richards (New York) was in the Chair, and the following papers were read:

Functional Anatomy

Professor A A Liebow (New Haven, Conn.)

Control of Breathing

Dr J H Comroe (San Francisco, Calif.)

Distribution of Ventilation and Blood Flow

Dr H Rahn (Buffalo, N.Y.)

Gas Uptake and Diffusing Capacity

Dr R E Forster (Philadelphia, Pa.)

Mechanics of Breathing

Dr J Mead (Boston, Mass.)

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(Continued from p 736)

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Section of Medicine

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Cardiac Septal Defects

Dr D Evan Bedford (London)
Atrial Septal Defect

Atrial septal defect (A.S.D.) is the most frequent single congenital malformation of the heart encountered in clinical practice. I will discuss A.S.D. occurring as an isolated or as the main lesion, and exclude A.S.D. combined with other major malformations.

Before the War the diagnosis of A.S.D. depended mainly on the radiological features and could only be made with assurance in adults with gross changes in the heart and pulmonary vessels. The advent of cardiac catheterization enabled us to make the diagnosis with certainty in children before the occurrence of secondary cardiovascular changes. Catheterization proves the left-to-right shunt by demonstrating arterialized blood in the right atrium compared with the superior vena cava, and in the majority of cases the catheter can be passed through the defect into the left atrium.

To-day we can almost always make the diagnosis on ordinary routine clinical findings alone. Nevertheless, catheterization provides valuable information as to the volume of the shunt and the pulmonary arterial pressure, so that we always employ it before surgery.

Anatomical Varieties of A.S.D.

Once closure of A.S.D.s by open heart surgery became feasible, the need arose to recognize the anatomical variety of the defect before operation, and to-day we can usually do this.

Secundum (fossa ovalis) defects: About 85% of A.S.D.s occupy the fossa ovalis, and sometimes they extend below the fossa lying astride the orifice of the inferior vena cava which thus opens into both atria. If the defect has no posterior margin, the right pulmonary veins open into both atria also.

Superior caval (sinus venosus) defects: About 6% of A.S.D.s lie above and separate from the fossa ovalis, immediately below the orifice of the superior vena cava (S.V.C.) which thus opens into both atria. In this variety, the right pul-

monary veins are always abnormal. Usually the upper vein opens into the S.V.C., the middle vein or veins into one or both atria level with the septal defect and the lower vein into the left atrium.

Atrioventricular (A-V) or primum defects: Excluding patients who die in infancy, about 10% of A.S.D.s overlie the ventricular septum and attached mitral and tricuspid valves. The anterior cusp of the mitral valve is almost always cleft or deformed, and sometimes the septal cusp of the tricuspid is similarly affected. When the cleft in these two valve cusps is continuous across the ventricular septum there is a common A-V canal with anterior and posterior leaflets and the upper part of the ventricular septum is defective also. When the ventricular septal defect is large, death in infancy is the rule and such cases are rarely seen outside a children's hospital; but where there is no gross ventricular shunt survival to adult life is possible.

Hæmodynamics

An A.S.D. of average size, say 3 cm in diameter, transforms the two atria into a physiological single chamber from which blood takes the path of least resistance into the more distensible right ventricle rather than the left. This left-to-right shunt increases the output of the right ventricle so that the pulmonary flow may be two to four times the systemic and attain a volume of 20 l. a minute or more. Vasodilatation in the lungs usually prevents any serious rise of pulmonary arterial pressure, but in about 12% of cases obliterative changes develop in the small vessels which increase the vascular resistance and this results in obstructive pulmonary hypertension.

Cardiovascular Changes

The increased pulmonary circulation leads to hypertrophy and dilatation of the right atrium and ventricle and to dilatation of the pulmonary trunk and its main branches, which may eventually become atheromatous or even calcified. Pulmonary hypertension often provokes thrombosis of larger arterial branches which is one of the

most serious complications of A.S.D. At birth the atrial shunt is probably small, but as the right ventricle involutes so the shunt increases and secondary changes in the heart develop gradually.

Rheumatic mitral disease may complicate atrial septal defect in adults, and 8·5% of our 222 surgical cases had some degree of mitral stenosis at operation (Table 2).

Clinical Features

In the last five years, my colleagues and I have investigated 400 cases of A.S.D. in the Department of Cardiology at the Middlesex Hospital and in my clinic at the National Heart Hospital and 252 of these have now been operated on by Mr Holmes Sellors and his colleagues. The age and sex incidence is shown in Table 1. Female predominance is greater in secundum than in primum defects in which post-mortem statistics show the sex incidence to be about equal.

Table 1

Age and sex incidence in 400 cases (252 surgical) of atrial septal defect, comprising 346 cases of secundum defect (222 surgical) and 54 cases of primum defect (30 surgical)

<i>Sex</i>							
Secundum type		Primum type					
<i>Age</i>							
Years	0-9	10-19	20-29	30-39	40-49	50-59	60+
Secundum	41	82	73	64	49	32	5
Primum	11	22	9	5	2	2	3

In an average case of secundum defect the important clinical signs are as follows: a right ventricular apical impulse, a pulmonary systolic ejection murmur, a widely split second sound which varies little with respiration and a short delayed diastolic murmur due to increased flow through the tricuspid valve. The essential radiological features comprise right atrial and ventricular enlargement, gross dilatation of the pulmonary trunk and main branches and generalized pulmonary plethora; the aorta is small. These radiological changes may be little evident in children and are best seen in older adult patients.

The ECG shows in almost all cases a partial or complete right bundle branch block pattern, with the so-called RSR configuration in lead V₁.

Pulmonary hypertension modifies the usual clinical signs. The pulmonary systolic murmur is less evident, the second sound is more closely split and accentuated, there is often a systolic ejection click and pulmonary incompetence is common, but the tricuspid diastolic murmur is usually absent. A prominent *a* wave appears in the jugular venous pulse. The ECG shows a gross right ventricular hypertrophy pattern in the chest leads.

Mitral stenosis combined with A.S.D. is very difficult to diagnose as its characteristic murmurs are much subdued and left atrial enlargement is

Table 2

Incidence of complications in 400 cases of atrial septal defect, including those found at operation in 222 secundum defects

	<i>Secundum</i> 346 cases	<i>Primum</i> 54 cases
Gross enlargement (Cardio-thoracic ratio over 60%)	31%	33%
Congestive failure	12·4%	11%
Atrial fibrillation or flutter	12%	7·4%
Pulmonary hypertension (over 50 mm Hg systolic)	16·4%	13%
<i>Surgical</i> <i>222 cases</i>		
Mitral stenosis	19 (8·5%)	
Mitral incompetence	4	
Pulmonary stenosis		10 (4·5%)
Superior caval defects		13 (5·8%)
Other anomalous pulmonary veins		3
Left S.V.C.		8 (3·6%)

Table 3

Incidence of complications in different age groups in 300 cases of secundum type defect

Years	Cases	1-9	10-19	20-29	30-39	40-49	50-59	60+
		41	74	61	50	43	27	4
<i>Incidence of complications (percentage)</i>								
CTR over 60%		14·6	6·7	28	30	65	70	100
Pulmonary hypertension		7·3	2·7	8·2	30	49	22	50
Congestive failure		7·4	1·3	11·5	16	35	52	50
Atrial fibrillation				3·2	4	30	33	25

less evident than usual in radiographs. It may be suspected in an adult when there is a rheumatic history, a grossly enlarged heart, atrial fibrillation, a raised jugular venous pressure and bifid P waves in the ECG. Occasionally, Kerley's lines are seen in radiographs.

Superior caval defects can usually be diagnosed. There is an ampullary dilatation of the superior vena cava just above the right atrium, the anomalous right pulmonary veins can usually be entered at catheterization and they can also be demonstrated by tomography or better by angiography.

In *primum defects*, the characteristic signs are due to mitral valve deformity. There is a pansystolic murmur and sometimes a thrill due to mitral incompetence, and the delayed diastolic murmur is longer, louder and better heard at the apex than in secundum defects.

The ECG shows left axis deviation combined with a right bundle branch block pattern in the chest leads and this type of curve occurred in 33 out of 34 of my primum defects verified at operation or necropsy. A prolonged P-R interval is common and bifid P wave of mitral type may occur. The frontal vectorcardiogram is also distinctive.

It is now possible to diagnose the three main anatomical varieties of A.S.D. with considerable accuracy. We have not yet failed to recognize a

primum defect before surgery. It is very important to diagnose them as their repair requires extracorporeal circulation, whereas we do the secundum defects under hypothermia.

Clinical Course

The ordinary fossa ovalis secundum defect is a relatively benign lesion. A few patients die in infancy from pneumonia, otherwise they usually remain free from serious cardiac symptoms until adult life. Between the ages of 20 and 40 cardiac symptoms begin to appear, and by the age of 40 about half are seriously handicapped. Gross cardiac enlargement, atrial fibrillation, pulmonary hypertension and congestive failure become increasingly common after the age of 30 (see Tables 2 and 3).

The average age at death is usually given as about 35. Of 6 non-surgical deaths in my series, the average age was 40; all of them had pulmonary hypertension. Of our 9 surgical deaths, 7 were aged over 40 and their expectation of life was probably short.

In primum defects, the outlook is much less favourable. Most cases of common A-V canal die before the age of 4 years and many of the less complicated primum defects die before 30, but a few survive longer.

Indications for Surgical Treatment

The proper time to close an A.S.D. is before the age of 20, when the heart and pulmonary vessels are relatively intact, and before the occurrence of symptoms. The operative mortality in such favourable cases is now extremely low, less than 1% in our surgical series, so that surgical closure as a routine is justified, unless the shunt is extremely small.

In those aged over 40 with unfavourable features such as gross cardiac enlargement, pulmonary hypertension, atrial fibrillation, mitral stenosis or congestive failure, the operative mortality was 11% but the need for surgery is greater and the majority of such patients are willing to accept the risks. The only absolute contra-indication to surgery is obstructive pulmonary hypertension with a vascular resistance exceeding 4 to 5 units, and a left-to-right shunt of less than 2 to 1. In such cases the mortality is prohibitive and the few who may survive operation are unlikely to gain much benefit.

The results of surgery in secundum defects have generally been most satisfactory but there is a definite post-operative morbidity mainly due to atrial flutter which resists treatment. Post-operative flutter occurred in 15% of our patients, in one-third of whom it has proved resistant to treatment.

In the case of primum defects we do not yet

know the indications for surgery, but the operative hazard is greater (16% in our 31 cases), and the benefit is often less than in the case of secundum defects, though some cases do extremely well. Further experience will probably enable us to select those most likely to benefit from surgery and to reduce the operative mortality.

Mr T Holmes Sellors (London) Atrial Septal Defects

Our policy for the treatment of atrial septal defects has been to close them under direct vision, using for the secundum variety hypothermia at 30°C, and for ostium primum lesions normothermic perfusion. Since ostium secundum lesions can be closed by direct suture within ten minutes we feel that the technical simplicity of 30°C hypothermia, which we have now used in 400-500 cases, has advantages over extracorporeal circulation methods which involve heparinization, a considerable volume of donor blood and an elaborate apparatus. The advantage of 30°C hypothermia is its simplicity and relative freedom from complications; its limitation is the time allowed for circulatory arrest - ten minutes.

If all secundum defects are to be treated under hypothermia it is essential to ensure accurate diagnosis and distinction between the two varieties. In the present series no primum defect was exposed under hypothermia (except for 2 cases before perfusion was available). It is a tribute to Dr Evan Bedford and his fellow cardiologists that they have been able to establish such a high standard of diagnosis in 300 cases (Table I).

Secundum Defects

Secundum defects are treated by direct suture under 30°C hypothermia, which is produced by surface cooling in the method developed by Sellick (1957, *Lancet* i, 443) from the original technique of Swan. Over 270 operations have been undertaken by this method without serious problems from the use of hypothermia.

Secundum defects fall into 3 main groups, over 200 of them being of the *foramen ovale variety*. The opening may involve the whole area of the fossa ovalis or it may be partial with fenestration or with remnants of the ovale valve. The second group, which is strictly a sub-division of the ovale type, is called the *inferior caval form*. This has no

Table I
Atrial Septal Defects: 303 operation cases

Ostium primum	31
Ostium secundum	272
Ovale type	190
I.V.C. type	62
S.V.C. or sinus venosus	20

lower border so that the inferior vena cava opens directly into both atria. The absence of a lower margin is of surgical importance since inaccurate closure may lead to deflection of the blood stream into the left atrium with resultant cyanosis. The third type is the *sinus venosus* or superior caval variety. This is a small defect in the upper part of the atrial septum, and it is the only type that is regularly associated with anomalous right pulmonary venous drainage. We have only encountered one case of anomalous drainage not associated with this form of defect. It may not always be possible to close the defect and deflect the right pulmonary veins into the left atrium, but in most cases an effective closure can be achieved and most of the venous drainage deflected. Where there would be any risk of narrowing the superior vena cava it is better to leave one vein to drain into the right side. The residual shunt is not significant.

The defects are closed by direct suture with non-absorbable material, using a double row of interlocking continuous stitches. In the case of inferior caval defects the first stitch at the lower end has to be inserted so that it takes in not only both edges but also the posterior wall of the left atrium. This avoids deflecting the blood from the inferior cava into the left atrium. Central cyanosis and clubbing occurred in 4 cases from failure to observe this point and correction at the same operation or later was necessary. In sinus venosus defects it is usually possible to place the suture line so that the veins are directed into the defect and into the left atrium without endangering the superior vena cava. If one of the anomalous veins enters high in the atrium or into the vena cava it should be left alone unless a left superior vena cava is present. This permits division of the right superior vena cava which facilitates the repair. We do not recommend anastomoses or replacement of veins in these cases.

No case of secundum defect has required a patch or prosthesis for its closure and there has been no observed instance of breakdown or tearing out of the suture line. This is largely due to the fact that once the defect is closed and the shunt abolished the distension of the right atrium is reduced and the strain on the suture line is lessened. Of 65 patients catheterized after operation 87% were shown to be completely closed. In 7 cases, operated on in the early days of open heart surgery, a small residual shunt was observed.

Table 2

Atrial septal defects: secundum defects—results

	Cases	Deaths
Total	272	9 (3.3%)
'Good risk'	206	1 (0.5%)
'Bad risk'	66	8 (12%)

In very large or total defects there were 4 cases of heart block, presumably from trauma or traction in the region of the A-V node. There have also been a number of cases of atrial fibrillation and flutter. Flutter occurred in 34 patients and persisted in 8 of these. These were thought to be produced by damage to the atrial wall, but there seems no relationship between the size or the placing of the incision and the incidence of this complication. Ventricular fibrillation has been rare so long as the body temperature did not fall below 29.5°C. There were 12 cases and most of these reverted with defibrillation or warming, but 3 patients died.

The overall operative mortality in 272 cases was 3.3%. In 206 good risk cases it was 0.5%. In patients with pulmonary hypertension, very large hearts, a history of failure or added mitral stenosis (the bad risk group) the mortality was much higher, i.e. 12% amongst 66 cases. There were two deaths in 18 sinus venosus defects—one from an overlooked mitral stenosis (Table 2).

Primum Defects

The surgery of ostium primum defects is a more complicated procedure than of the secundum form. Table 3 shows the different anatomical types. These defects are treated by open heart surgery using perfusion with full body flow (Mayo Gibbon apparatus) and without cardiac arrest.

The defect is invariably associated with a cleft or deformed mitral valve. To overcome valvular insufficiency the 'cleft' has to be closed by suture before the actual defect is occluded. The defect presents as a crescentic opening with a well-defined upper atrial edge and the mitral-tricuspid valves over the ventricular septum as a 'lower' border. Direct suture fails to maintain closure and a patch or prosthesis is required to obliterate the defect (Fig 1).

In 3 instances deaths were due to perfusion errors or to some technical problem, one was caused by reactionary haemorrhage, the others were due to clotting difficulties. There were two later deaths from subacute bacterial endocarditis. There have been 4 cases of heart block (one of them temporary) presumably due to traction or

Table 3
Atrial Septal Defects: Ostium Primum Defects—31 Cases

Anatomical	Cleft mitral valve	30
	Cleft mitral valve plus cleft tricuspid	10
	Cleft mitral valve plus V.S.D.	3
	Associated secundum defect	6
Surgical	Left S.V.C.	4
	Direct suture	10
Results	Patch to defect	21
	Operative deaths	3
	Later deaths (Subacute bacterial endocarditis)	2

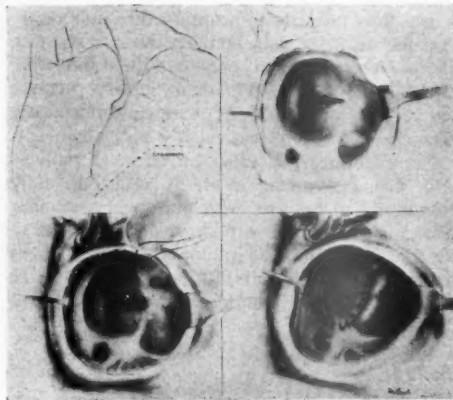


Fig 1 Ostium primum defect. Top right: Appearance with the atrium open, the deformed mitral valve being visible through the crescentic opening. Bottom left: The cleft mitral valve has been sutured. Bottom right: Closure of the defect by a patch

haematoma in the region of the node.

A long-term analysis of the results of surgery in primum defects is not yet practicable, but several impressions have been gained from clinical and catheter findings. In the early cases in which a patch was not used there was a high incidence of breakdown of the suture line. Out of the first 7 cases that were catheterized there was evidence of an appreciable shunt in 3. The later cases have been much more satisfactory, but complete closure of the shunt is not always obtained. Without a detailed study it is not possible to say how effective the restoration of valve function has been, though the improvement or abolition of the mitral murmurs has been achieved in most cases. In general there is considerable benefit to the heart action with reduction in its size and diminution of right heart activity, and coupled with this is an improvement in the patient's general condition.

Dr J F Goodwin (London) Ventricular Septal Defect

The indications for surgical treatment of ventricular septal defect must be considered in the light of the prognosis without surgery. It is generally acknowledged that the prognosis for large defects in the first year of life is poor, death from heart failure and pulmonary hypertension, and from respiratory infections, being common (Reinhold 1958, Marquis 1950, Zacharioudakis *et al.* 1957, Bonham-Carter 1959, personal communication, Morgan *et al.* 1960). After the age of 2 years, children often improve and may be quite active,

although respiratory infections are frequent and physique poor. Pulmonary vascular disease and pulmonary hypertension rarely increase in infancy (Downing 1959, Nadas 1960), but may do so in later life (Keith *et al.* 1958, Brotmacher & Campbell 1958).

The ultimate prognosis of ventricular septal defect is obscure, for few adult patients are seen either in life or at necropsy (Wood *et al.* 1954, Brotmacher & Campbell 1958). There are several possible reasons for this: the defect may close in early life (Evans *et al.* 1960), the condition may be transformed into the tetralogy of Fallot as a result of progressive infundibular obstruction (Gasul *et al.* 1957, Brotmacher & Campbell, 1958), and defects may be missed at necropsy if small and multiple and situated in the muscular portion of the septum. In patients with very large defects and pulmonary hypertension, surgical closure is indicated to prolong life, but in those with medium or small defects, the threat to life without operation is less certain. But in those children who are physically handicapped by a large defect, closure of the defect results in improvement in physique and freedom from respiratory infections.

The conclusions to be presented are based upon the results in 95 patients operated upon at Hammersmith Hospital by Mr W P Cleland, Mr H H Bentall and Mr L L Bromley under total cardiopulmonary bypass using the Melrose-N.E.P. pump oxygenator. The medical assessment and after-care has been carried out with my colleague Dr A Hollman, who is associated with me in this report.

The patients' ages ranged from 2 to 56 years, the majority being aged 5 to 10 years. Only 7 patients were over the age of 20 years. Operation under the age of 2 years carries a high mortality and we have not attempted operation in this age group.

The indications for operation must be considered in the light of its risks and the results achieved (Table I). The mortality rate of 13·6% was found to be related to four main factors: pre-existing pulmonary vascular disease, significant associated cardiac lesions, complete heart block occurring during the closure of the defect and persisting, and reopening of the defect. The best results were found in patients who had a satisfactory fall in right ventricular pressure immediately after closure of the defect and in

Table I
Ventricular septal defect—first 95 patients

Results of Operation		
Died	13 patients	
Alive and well	82 patients	{ 95
Residual left-to-right shunt	18 patients	{ Appreciable 7 Minimal 11

whom heart block did not occur. Residual small left-to-right shunts indicating opening of the defect did not occasion any anxiety after the first week following the operation. Of the 82 patients alive and well after the operation, 18 had some degree of left-to-right shunt. This aspect will be considered further by Mr Cleland and Dr Hollman.

In assessing patients for operation the degree of pulmonary vascular disease was of the greatest importance. Appreciable pulmonary vascular disorder is unusual in patients with small defects, who may be free of symptoms. Patients with a ratio of pulmonary to systemic blood flow of less than 1.5:1 were not considered to require operation unless symptoms were present, pulmonary hypertension was a feature, or the physical and other signs suggested that the flow ratio had been under-estimated by catheterization. Patients with medium-sized or large defects usually had a history of feeding difficulties and respiratory infections in infancy, the respiratory infections often persisting into childhood, being associated with poor physique and stature, although physical activity was often but slightly impaired.

Table 2 shows the mortality related to pulmonary vascular disease, and indicates that mortality was significantly higher when the pulmonary vascular resistance measured at catheterization exceeded 8 units. It also shows that a high resistance does not necessarily contraindicate operation, for 75% of these patients were successfully operated upon.

Table 2
Ventricular septal defect—first 95 patients:
Pulmonary vascular resistance (normal 0–2 units) in 90 patients

	0–8 units	> 8 units	Total
Patients	66	24	90
Deaths	6	7	13

$$\chi^2 = 3.984$$

The physical signs provided the best guide to the degree of pulmonary vascular disease; in particular the length of the systolic murmur of the septal defect contrasted well with the pulmonary vascular resistance. A full-length murmur suggested a low resistance, and when this was accompanied by a long thrill, a left ventricular thrusting cardiac impulse, a mid-diastolic apical murmur due to increased flow through the mitral valve and a cardiogram showing deep Q waves in left precordial leads, with tall R waves and left axis deviation, a good result could be confidently predicted, provided no serious associated cardiac lesions were present. By contrast, a short ejection systolic murmur, a loud and narrowly split second heart sound, poor thrill and absent

mitral flow murmur indicated severe pulmonary vascular disorder, with an operative risk of up to 25%. However, such patients often did well, especially when the pulmonary artery pressure fell to 50% or less of the systemic immediately after closure of the defect.

Complete heart block occurred in 15 patients and was permanent in 4. It occurred more commonly in patients with pulmonary vascular disease, and in those with larger defects. Three of the 4 patients who died in block had a pulmonary resistance above 5 units, further evidence of the added hazard of pulmonary vascular disease (Table 3).

Table 3
Ventricular septal defect—first 95 patients:
Details of complete heart block in 15 patients

Complete heart block:	Transient	11
	Permanent	4
	Fatal	4
Pulmonary arteriolar resistance (PAR) = 0 to 8 units in 8 patients (In 4 fatal cases PAR was 10, 12, 5 and 7 units respectively)		
Size of defect (sq. cm per sq. m body surface area) (1 not recorded)		
1 or less than 1 = 2 patients		
1 to 2 = 3 patients		
2 to 4 = 7 patients		
Greater than 4 = 2 patients		

Defect still open (residual shunt after operation): 4 cases

Associated cardiac lesions were common (Table 4). Those in Group A constituted an appreciable additional hazard, for nearly half

Table 4
Ventricular septal defect: 55 associated lesions and complex defects

(1)	<i>Associated Lesions</i>	<i>No. of Patients</i>
A.	<i>Important</i>	
	Patent ductus arteriosus	11
	Aortic valve disease	9
	Mitral valve disease	7
	Anomalous coronary artery	1
B.	<i>Less important</i>	
	Infundibular or valvular pulmonary stenosis	10
	Peripheral pulmonary stenosis	2
	Atrial septal defect	3
(2)	<i>Complex Ventricular Defects</i>	
	Multiple defects	7
	Single ventricle	1
	Corrected transposition	3
	(Ruptured sinus of Valsalva	1)

of those who died had some severe additional lesion (Table 5). It is clear that ventricular septal defect is by no means always a simple lesion and that the detection of associated anomalies is of the greatest importance in assessment for operation. A full clinical study of each patient, including catheterization, selective right ventricular

Table 5
Ventricular septal defect—first 95 patients
Patients who died (total 13)

Case No.	Cause of death	Pulmonary arteriolar resistance (units)	Pulmonary systemic flow ratio	Size of defect (sq.cm per sq.m body surface)
1	Haemorrhage. Pulmonary hypertension	9	1.5	2.5
9	Missed defect. Pulmonary hypertension. Complete heart block	10	2.6	2.1
14	Haemorrhage	20	2.0	2.5
15	Haemorrhage from ductus	18	1.3	1.17
23	Sudden ? pulmonary hypertension	9	1.8	0.9
34	Anomalous coronary artery	2	1.9	1.4
40	Defect reopened	2	5	2.3
42	Complete heart block. Corrected transposition and mitral stenosis	5	2.2	1.9
52	Complete heart block	7	2	3.5
53	Aortic incompetence	1	2.2	2.5
54	Pulmonary hypertension and haemorrhage from ductus	6	4	1.1
77	? Pulmonary hypertension	14	1.7	2.63
85	Complete heart block (mitral incompetence)	12	2	5.5

angiography and sometimes aortography, is most important.

Patients with pulmonary: systemic flow ratio of less than 1.5:1, a pulmonary vascular resistance above 10 units and a right-to-left shunt were rejected for operation on the grounds of severe pulmonary vascular disorder.

Patients with a low pulmonary resistance and no severe added lesions may confidently be advised to undergo surgery, the risks being in the region of 5% and the results most gratifying in terms of restoration of normal health. Patients with large left-to-right shunts and high pulmonary vascular resistance are in great need of operation but higher risks must be faced. The hazard of complete heart block is never completely absent and this must be taken into account before considering symptomless children with smaller defects, although persistent block has not been a feature of small defects in our series.

Acknowledgment: We are grateful to all those who have kindly referred patients, and in particular to Dr R E Bonham-Carter whose unfailing support and valuable advice have been of the greatest service.

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Mr W P Cleland (London)
Ventricular Septal Defects

I propose to exclude complicated defects, where the surgery is difficult and hazardous, and consider only the more straightforward ventricular septal defects. This will give an idea of what may be expected from surgery in the ordinary case. The majority of the patients have been operated on at Hammersmith Hospital by Mr H H Bentall, Mr L L Bromley and myself, but some have been operated on by me at the Brompton Hospital.

I have selected the first 100 patients in order to make analysis easy and to provide an adequate period of observation after operation. Table 1 shows the over-all results in these 100 patients.

Table 1
Ventricular septal defects

Total patients	100
Operative mortality	11
Later mortality	0
Alive with permanent heart block	3
Alive with significant residual shunt	9
Alive and well	77

The operative mortality was 11% and there have been no later deaths. Three are alive with a permanent heart block and 9 are alive with a significant residual shunt. 77 are alive and well from the point of view of their ventricular defect but some of them are disabled from associated aortic valve disease and mitral valve disease which could not be corrected at the time of the operation.

Fig 1 depicts diagrammatically the interventricular septum as viewed from the right ventricle. The position of the crista supraventricularis (B), to which these defects are related, should be noted: A, C, E and F are the common sites of the defects; C is the common infracristal type and it is this defect whose posterior angle lies in close relationship to the atrioventricular bundle as it passes from the A-V node to the ventricles.

Table 2 shows the incidence of the various types of defect. 70% are infracristal and together with a further 11 tricuspid defects make a total of 80% which are in close relationship to the A-V bundle and so are liable to the complication of heart block after operation.

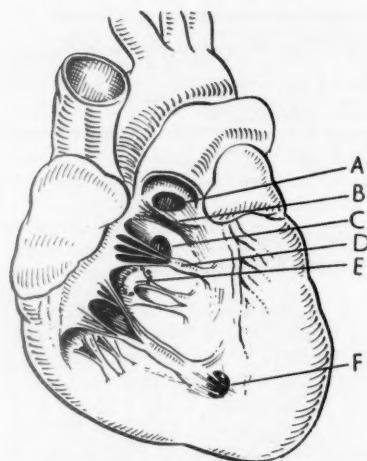


Fig 1 Diagrammatic view of the ventricular septum from the right side: A, Supracristal defect. B, Crista supraventricularis. C, Infracristal defect. D, Papillary muscle of the conus. E, Tricuspid defect. F, Muscular defect

Table 2

Ventricular septal defects

Incidence of defects at various sites

Infracristal	70
Tricuspid	11
Supracristal	6
Muscular	3
Fenestrated septum	2
Multiple defects	8

There were 6 supracristal defects and the majority of these have been associated with minor or moderate degrees of aortic incompetence.

There is a small but important group with a fenestrated septum with multiple communications between the two ventricles. This is an extremely difficult type to deal with surgically and both our patients have persistent shunts. Eight patients had multiple defects; it is very easy to overlook one or more of these multiple defects at the time of operation - an error which has occurred twice.

All the patients were operated on with the aid of extracorporeal circulation, using the Melrose/N.E.P. heart-lung machine.

The first 50 or thereabouts were done using potassium citrate arrest of the heart but the remainder were operated on with the body temperature reduced to 30°C associated with intermittent aortic clamping. We have not considered it necessary to reduce the temperature to the point where there is hypothermic arrest of the heart, nor have we been keen to employ anoxic arrest. We prefer to keep the heart beating reasonably well for two reasons - to be able to monitor the bundle and so determine whether heart block is imminent and to be able to determine accurately the effi-

ency of closure by maintaining a good ventricular beat throughout.

Wherever possible we try to close the defect by direct suture, but in larger defects, and particularly in those with fleshy muscular margins, we consider it wise to use a prosthesis. In 21 patients a patch of Teflon felt has been used to occlude the defect. A comparison between the two groups revealed no significant difference in the incidence of heart block or of residual shunt after closure.

Careful analysis of the pre-operative data has shown that the most important determination is the level of the pulmonary vascular resistance when assessing operative risks and ultimate prognosis.

Table 3 shows the effect of pulmonary vascular resistance on mortality and results.

There were 74 patients with a low resistance (less than 8 units) with 5 deaths, 8 with heart block (2 permanently), 5 with residual shunts and 80% gave a good final result. In the higher range of resistance (over 8 units) there were 26 patients with a 21% mortality but 54% finally had a good result.

Table 3

Ventricular septal defects

Results related to pulmonary vascular resistance

Resistance	Total	Mortality	Heart block	Residual shunt	Good result
1-8 units	74	5 (7%)	1 died 8 { 2 permanent 5 temporary	5	60 (80%)
Over 8 units	26	6 (21.5%)	2 died 6 { 1 permanent 3 temporary	4	14 (54%)

At the time of the operation, the most important single estimation indicating success, or possible failure, is the level of the pulmonary artery pressure after closure of the defect. Table 4 shows the effect on the results of the post-operative level of the pulmonary artery pressure (expressed as a percentage of the systemic blood pressure).

There were 16 patients in whom the pulmonary artery pressure was above 50% of the systemic pressure after operation. Of these 16, 6 died and in only 8 was there finally a good result. This contrasts with 3 deaths among 82 patients in whom the

Table 4

Ventricular septal defects

Results related to fall in pulmonary artery pressure

Post-operative pulmonary artery pressure	Total	Died	Block	Residual shunt	Good result
More than 50% of systemic	16	6	3	2	8
Less than 50% of systemic	82	3	11	7	66

• Excluding 2 patients who died on the operating table.

Table 5
Ventricular septal defects: Factors contributing towards death

	No of patients
Hæmorrhage	2
Heart block	1
Respiratory difficulties	2
Aortic incompetence	1
Mitral incompetence and block	1
Unrecognised second defect and block	1
Anomalous coronary arteries	1
Torn ductus	1

pulmonary artery pressure was below 50% of the systemic; 66 of these patients did well.

Table 5 indicates the factors which we consider were basically responsible for death amongst the 11 patients who died after operation. There is no one very important cause of death. Heart block was primarily responsible for the death of only one patient, although in two others it was present in addition to other serious handicaps. In only two patients were respiratory difficulties basically responsible for death.

In the post-operative period there are two main concerns about the patient. The first is the occurrence of complete heart block and the second is the persistence of a left-to-right shunt. That these are complementary will be seen from Table 8 – an increase in the incidence of heart block being associated with a reduced incidence of persistent shunt and vice versa.

There is a constant conflict in the surgeon's mind between effecting complete and permanent closure yet avoiding damage to the bundle of His. Table 6 shows 14 cases in which complete heart block was produced. Three of these died, but only one was directly due to the block. Only 3 have permanent block and they have survived for one year or more. The other 8 patients reverted to sinus rhythm after the period stated. Although sinus rhythm appeared six weeks after operation in one instance, reversion rarely occurs after three weeks. Twelve of the patients had large defects which were difficult to close and 6 had a high pulmonary resistance.

Table 7 shows patients who had a significant residual shunt as assessed some months after operation. There was a slightly higher incidence where the defect was closed with a patch but this may merely be due to the fact that these were

Table 6
Ventricular septal defects: Complete heart block

14 cases	{ 3 deaths 3 permanent 8 temporary – 2 hours, 4 hours, 1 day, 4 days, 10 days, 14 days, 21 days, 42 days
12 had defects of over 2 cm diameter	
6 had a high pulmonary vascular resistance	

Table 7
Ventricular septal defects: Residual shunt (9 patients)

Defect closed by direct suture	6 out of 79
Defect closed by Teflon patch	3 out of 21
Six of the patients had either large or multiple defects	

larger and more difficult defects to close. Six of the patients with residual shunts had either very large or multiple defects.

There were 11 other patients who had clinical signs suggesting a shunt but investigations have failed to provide confirmation.

Table 8 shows the results for the years 1958, 1959 and 1960. There was a gratifying fall in mortality in 1960 to 2·2%.

Table 8
Ventricular septal defects: Results 1958–1960

	Total	Died	Shunts	Block
1958	26	4 (16%)	2 (8%)	3 (12%)
1959	30	6 (19%)	2 (6%)	6 (18%)
1960	44	1 (2·2%)	5 (11%)	5 (11%)
Totals	100	11	9	14 (3 permanent)

From the surgeon's point of view, the hazard is mainly that of a difficult anatomy, particularly that of the large defects which plunge deeply down towards the tricuspid annulus in which the bundle is in great peril and where closure can only be effected by implicating part of the tricuspid valve. If complete closure can be achieved without the production of heart block the outlook is excellent with remarkable improvement in the clinical condition of the patient especially where there are no additional complicating lesions.

This survey fails to support the gloomy outlook which has been held for the higher resistance group. The mortality rate in this group is not prohibitive and in 50% there were very satisfactory late results.

Dr A Hollman (London)

The Status of the Patient after Leaving Hospital

Improvement in physical condition: The great majority of patients notice increased physical vigour with lessening or disappearance of breathlessness and fatigue after operation. This occurs even in those who had no symptoms before the operation – presumably because they were leading rather restricted lives.

Auscultatory signs: After operation a systolic murmur may still be heard, but only in a minority of cases does this mean that the ventricular defect is still open, as shown in Table 1. Fifteen out of 18 soft (Grade I) systolic murmurs had no detectable cause and were classed, therefore, as being innocent. Of Grade II murmurs slightly

Table 1

Causes of persistent bruit in 85 patients after operation for ventricular septal defect

	Intensity of systolic bruit (post-operative)				
	Absent	Grade I	Grade II	Grade III	Grade IV
Total	15	18	28	21	3
Defect open	0	0	4	13	1
Other lesions (pulmonary stenosis, aortic stenosis, mitral incompetence, complete heart block)	0	3	8	5	2
'Innocent' murmurs	0	15	16	3	0

over half were innocent, but over a third were due to an associated cardiac lesion such as pulmonary stenosis. The loud murmurs (Grades III and IV), often with a thrill, were due in 60% to a residual shunt, and only a few were innocent. Persistent left-to-right shunts were found in 18, but these were large only in 2 patients. A typical example of a small residual shunt is seen in Fig 1. There is only a small rise in oxygen saturation between right atrium and right ventricle and it is the dye dilution curve that indicates definitely that a shunt is present.

In 5 patients an early diastolic murmur, almost certainly aortic, developed post-operatively, the onset varying from a few weeks to several months. In 1 patient there was also a gradual appearance of an aortic systolic murmur. The genesis of these bruits is uncertain but they may

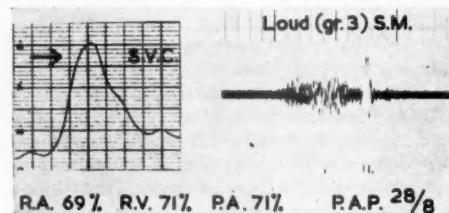


Fig 1 Dye dilution curve, phonocardiogram, oxygen saturation at cardiac catheterization, and pulmonary artery pressure in a 13-year-old patient two years after operation. It shows that the loud persistent systolic murmur may be due to a barely detectable residual shunt

be due to fibrosis related to the sutures in or near the aortic ring.

Relief of pulmonary hypertension: Several of our patients have been catheterized up to two years

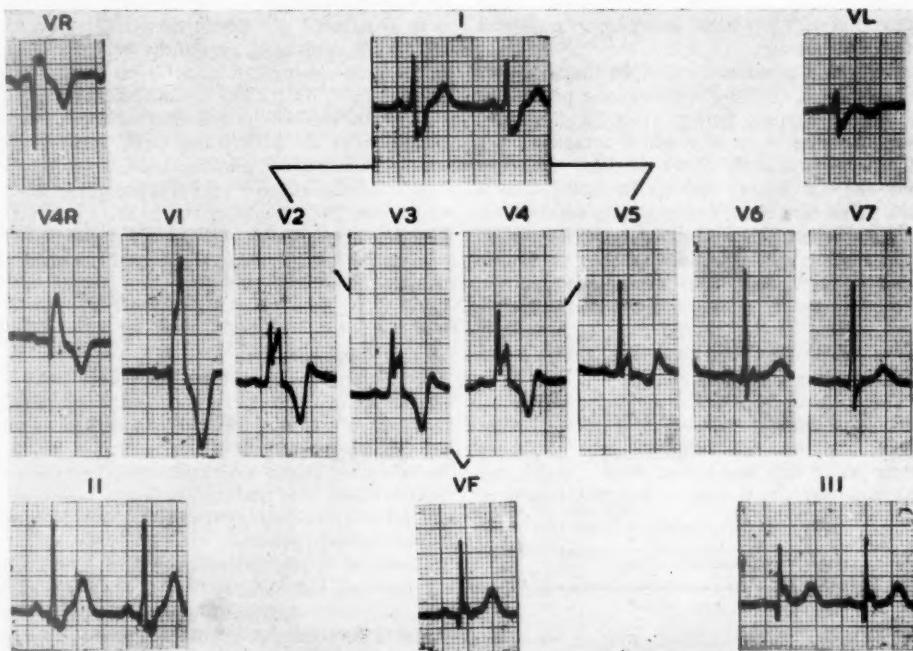


Fig 2 Electrocardiogram six months after repair of ventricular septal defect in a 7-year-old patient showing complete right bundle branch block and extensive T-wave inversion

Table 2

Relief of pulmonary hypertension by closure of V.S.D.

Pulmonary artery pressure (mm Hg)

Catheter	On table	Catheter
pre-op.	post-op.	post-op.
42/20	26/19	32/15
60/30	27/20	40/10
75/55	42/32	50/20
83/48	30/15	40/11
120/67	33/17	32/8

after operation, and the results in 5 patients are shown in Table 2. The relief of pulmonary hypertension occurs when the defect is closed, and there

is no evidence, on these figures, of *late* relief of the residual pulmonary hypertension due to gradual resolution of organic pulmonary vascular changes.

Changes in the electrocardiogram: Nearly all the patients developed right bundle branch block after operation, the main exception being those with supracristal defects. In many patients the branch block is complete, and is associated with striking T-wave inversion from V_1 to V_5 or further. Although these changes look unpleasant (Fig 2) there is no detectable cardiac disability. In a few patients followed for a year or more after operation the ECG changes have tended to regress.

Meeting March 28 1961

Isotopes in Medicine**Professor G M Wilson (Sheffield)****Radioactive Isotopes in Diagnosis**

Radioactive isotopes have been used for over ten years as investigative agents in clinical medicine and have been employed as aids to diagnosis in a very wide variety of conditions. Certain general principles underlie their use in the study of disease processes. The tissues of the body handle in the same way the naturally occurring form and the radioactive isotope of an element. The isotope can be readily identified, followed through the body and measured in body fluids and excreta by the characteristic radiations which it emits. The radioactive isotope may be administered in a simple inorganic form to trace an element naturally present, for example iodine. It may be incorporated in a complex molecule by synthesis outside the body and then administered in this form to trace the compound, for example ^{58}Co -labelled vitamin B_{12} . Certain elements are taken up by particular cells and bound relatively firmly: ^{51}Cr can be used to label red cells in this way and their survival in the blood stream can be followed. No clear distinction can be drawn between the diagnostic use of radioisotopes and their employment in clinical investigation and research. I review here their advantages and limitations in some thyroid, gastroenterological and haematological disorders.

Thyroid Disorders

The thyroid gland concentrates iodide from the plasma and utilizes it in the formation of the hormones thyroxine and triiodothyronine. The passage of iodide into the thyroid and its subsequent release in an organic protein-bound form can be traced by using a radioactive isotope of

iodine. Those in common use are ^{131}I and ^{132}I . The latter has a short half-life of 2.3 hours. This has the advantage that it gives only a small irradiation dose to the gland, but greatly restricts its clinical use. ^{131}I , with a half-life of eight days, is more generally useful but it should be employed in children only in exceptional circumstances. A great variety of clinical tests have been devised employing ^{131}I to assess thyroid function. The assumption is made that the distribution of the tracer dose between the thyroid, blood and urine reflects the activity of the gland in the synthesis and secretion of hormone. The interpretation of the tests is usually straightforward, hypothyroidism being associated with a decrease in thyroidal uptake of ^{131}I and hyperthyroidism with an increased uptake and passage of a higher fraction of the dose into the blood in protein bound form (P.B. ^{131}I). No clear-cut boundary exists between the normal and the hypothyroid state. Thyrotoxicosis is more readily distinguished, particularly if both the thyroid uptake and the P.B. ^{131}I are measured (Wayne 1954). However, changes in uptake of ^{131}I or concentration of P.B. ^{131}I do not necessarily indicate any alteration in thyroid hormone output. High uptakes may be encountered in non-toxic goitre and elevated P.B. ^{131}I values in Hashimoto's disease, although the rate of release of hormone may be within the normal range in both conditions. Most of the difficulties in interpreting the results of tracer tests arise from failure to recognize that the results are greatly influenced by the conditions under which the tests are performed. Thus, previous treatment with substances affecting hormone synthesis or the unwitting administra-

tion of excess iodide in some disguised form is a much commoner cause of error than are technical faults in the measurements.

Alimentary Disorders

Fat absorption: The analysis of faeces for fat content is tedious and unpleasant and it is not surprising that an attempt is being made to develop isotopic methods which may circumvent these difficulties. Triolein and oleic acid may be labelled with iodine-131 monochloride. The extent to which the iodine is absorbed from the alimentary canal after oral administration is determined by collecting the faeces and determining the proportions of the dose recovered in this way. The faeces can be collected in tins which are sealed and can be assayed for radioactivity without any further preparation. This is clearly much simpler than chemical analysis. The accuracy of the method depends amongst other things on the ^{131}I label remaining intact while the radio-iodinated triolein is in the alimentary canal and on the absence of secretion of any absorbed ^{131}I into the alimentary canal. Excess stable iodide is given to prevent thyroidal uptake of ^{131}I and to ensure that any ^{131}I released in the body is excreted in the urine. In normal subjects less than 5% of the dose is excreted in the faeces.

The radioiodinated triolein method of detecting steatorrhoea is still under investigation. Attempts to dispense with stool collections and to determine the result on measurements of blood or urine radioactivity have not so far proved successful. The general conclusion of most investigators is that the radioiodinated triolein test with faecal counting is a useful screening measure for detecting steatorrhoea but has definite limitations. Investigations are continuing into variables that may influence the results, such as the quantity and nature of the fat given with the triolein (Cox 1961, personal communication). At present there is no doubt that the chemical faecal fat determination is a more sensitive and reliable index of steatorrhoea (Pimparkar *et al.* 1960).

Protein-losing enteropathy: Recently it has been recognized that in some cases of hypoproteinæmia there may be an excessive loss of albumin into the alimentary canal. This may be demonstrated by the intravenous injection of ^{131}I -labelled human serum albumin and determining the fraction excreted in the faeces (Jarnum & Petersen 1961). ^{131}I -labelled PVP (polyvinylpyrrolidone) may be used in the same way; it has a molecular size similar to human serum albumin but is not so liable to destruction in the alimentary canal (Gordon 1959).

Hæmatological Disorders

^{58}Co -labelled vitamin B_{12} is now extensively used

for detecting abnormalities in the absorption of the vitamin. This investigation is certainly not required in the routine investigation of pernicious anaemia but is often requested because treatment has been started with vitamin B_{12} without an adequate hæmatological investigation. The absorption defect of pernicious anaemia persists even though the abnormalities in the blood and marrow have been corrected by vitamin B_{12} . A normal absorption test indicates that the patient does not suffer from pernicious anaemia. An oral dose of 0.5–1.0 µg of labelled B_{12} is given when the patient is fasting. The amount excreted in the faeces may be measured or alternatively a large (1 mg) parenteral dose of unlabelled vitamin B_{12} may be given at the same time as the oral tracer dose (Schilling 1953). This 'flushes' out in the urine a high proportion of any ^{58}Co -labelled vitamin B_{12} that has been absorbed. This method is more convenient as the urine collection lasts only twenty-four or forty-eight hours in contrast to several days of faecal collecting. Moreover the radiation hazard is considerably decreased as most of the dose of the radioisotope is excreted and not stored in the liver. It has the disadvantage of involving a parenteral dose of vitamin B_{12} , which might confuse subsequent hæmatological investigations in doubtful cases, but it is the simplest and most convenient method of assessing vitamin- B_{12} absorption, has been extensively employed and, apart from patients with renal disease affecting excretion, gives reliable results. Nevertheless, if a quantitative measure of vitamin- B_{12} absorption is required faecal counting is essential. The use of ^{58}Co -labelled vitamin B_{12} has added greatly to the precision of diagnosis in many unusual cases of megaloblastic anaemia, especially those in young patients in whom gastric hydrochloric acid secretion may not be impaired. It is also possible to detect with the radioactive test defective vitamin- B_{12} absorption before definite megaloblastic changes have appeared in the marrow and we have found the method particularly useful in studying anaemia associated with myxœdema (Tudhope & Wilson 1960).

^{51}Cr has been widely used for labelling red cells. The label is firmly secured in the red cell and it is thus possible to follow the life of the labelled cells in the blood stream. Though the method is simple, particularly in comparison with the Ashby technique, there are often many difficulties in the interpretation of the curves. Useful information may be obtained in the investigation of hæmatological disorders and of gastrointestinal haemorrhage (Hayter 1960). Surface counting over the liver and spleen gives an indication of the rate of accumulation of ^{51}Cr in these organs. The quantity in the spleen may become very large in hæmolytic anaemia.

Investigations with the isotope ^{59}Fe have afforded much information about iron absorption and metabolism and have greatly increased our understanding of the dynamic aspects of many blood disorders. From the viewpoint of clinical diagnosis they are most important in demonstrating the activity of erythropoietic tissue. With the use of ^{51}Cr and ^{59}Fe together, simultaneous measurements of red cell survival and marrow activity may be made. Surface counting over heart, liver, spleen and sacrum may provide qualitative information useful in determining the rates and sites of red cell production and destruction though the precise interpretation of the results may be difficult and occasionally unreliable in predicting the effect of splenectomy.

Radiation Exposure and Health Hazards

It is probable that internal irradiation of tissues from administered artificial radioactive isotopes carries the same dangers as an equivalent exposure to ionizing irradiation from an external source. In all diagnostic investigations the exposure should be kept as small as possible. Fortunately advances in design of equipment are enabling accurate measurements to be made with smaller doses of radioactivity. Particular care must be taken if the isotope is concentrated in one tissue or organ such as bone or thyroid and it is especially desirable to avoid exposure of infants and young children to irradiation. Clearly in each case the possible hazard and the value of the information that might be obtained from the investigation must be balanced.

Conclusion

Now that radioactive isotopes have been available for a considerable period it is becoming possible to estimate the contribution that they may make to clinical investigation. The progress of a new radioisotope technique often resembles that of a new drug. Early enthusiasm gives way to later disillusion and finally a balanced judgment is obtained. Isotopic methods give the most useful and reliable information when they are combined with chemical or other measurements. Like all other laboratory methods radioisotope techniques can never offer a shilling-in-the-slot diagnosis and the results must always be considered in relation to the clinical conditions.

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Dr E S Williams (London)

The Use of Isotopes in Medicine as an Investigative Technique

Dilution Analysis

Dilution analysis is a familiar procedure well used in medicine before nuclear physics made its impact. It includes the dilution method of determining a physiological space, for example, using a dye for estimating plasma volume or urea for total body water. The dye is merely a marker, or label, for the plasma, and its degree of dilution (when corrected) is a direct measure of the plasma volume.

Radioactive isotopes extend the method to include a range of physiological 'spaces' and also render the procedure easier and more accurate. Dilution can be applied to the assay of a compound provided a radioactive label can be incorporated in a separately prepared sample of the compound. Here the 'space' through which the dilution occurs is the total mass of the compound to be assayed rather than a geometrical space or a more abstract physiological space (Fig 1).

Activation Analysis

A recent annotation in the *Lancet* (1961) reviewed medical implications of the phenomenon of 'activation' when elements are exposed to bombardment by neutrons. Analysis by utilizing the phenomenon has only become possible since the advent of the high neutron flux of the nuclear reactor.

A sample of material, say a physiological fluid or a piece of tissue, is placed in the reactor. Many of the atomic nuclei in the sample are transformed into radioactive isotopes of the original element and hence their presence is manifested by the characteristic radiations. Theoretically analysis in terms of elements is thus possible without destruction of the sample but there are inherent limitations and technical difficulties limit

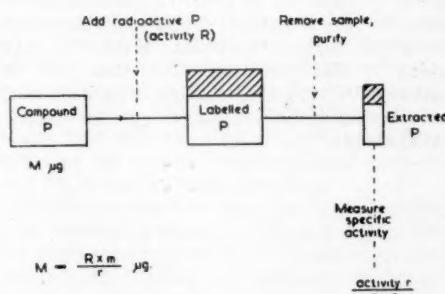


Fig 1 Dilution analysis

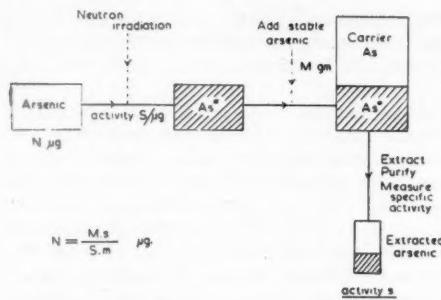


Fig 2 Activation analysis

the method still further. In spite of this, activation analysis is a powerful technique awaiting further development in the field of medicine, especially when nuclear reactors become part of the equipment of the larger research centres.

The method can be represented by a block diagram (Fig 2). The material to be assayed, typically a trace element such as arsenic, can be represented by the left hand block and the labelling of it is carried out by neutron-induced transformation to radioactive arsenic. Carrier arsenic is added before extraction and measurement of the specific activity of a sample.

Derivative Analysis

The dilution technique consists essentially of labelling a population by mixing into it marked additions; neutron activation goes a step farther and induces a transformation in the members of the population but it is limited to certain elements. To use an isotopic method for assaying a compound one can cause it to react with another, radioactively labelled, compound thus obtaining a radioactive derivative of the original material. Such a procedure is called derivative analysis.

Whitehead & Beale (1959) used this method for the assay of thyroxine (T_4) in blood. In order to 'activate' the thyroxine they added tritiated acetic anhydride thus producing the radioactive derivative ^3H -acetyl- T_4 . In order to eliminate errors caused by loss of material during purification and extraction carbon-14-labelled acetyl T_4 was added to the derivative. The ratio of ^3H activity to ^{14}C activity in a sample of pure material is a function of the amount of T_4 in the original blood sample.

This is another powerful tool for the detailed investigation of a number of medical problems. Its application requires complex chemical facilities so development of the method may be restricted.

Saturation Analysis

An elegant principle of analysis, which is, in certain cases, much simpler to apply than the last two methods, was proposed by Ekins (1961, in press) and called by him 'saturation analysis'. Three pre-requisites are necessary. The compound P to be assayed must be such that it will form a complex with a further substance Q; free P must be capable of physical separation from the P-Q complex; a supply of P must be available, radioactively labelled.

It will be appreciated that the first requirement is frequently met in biological systems: hormones which occur both free and in association with carrier proteins; proteins which occur free or as an antigen-antibody complex; vitamins which can also occur either free or in combination. A number of techniques are available to separate the free material from the complex: electrophoresis, chromatography and dialysis, to mention but three.

Ekins (1960) applied the principle to thyroxine assay and evolved a procedure which is now in routine hospital use. He predicted that it could be used for the assay of insulin, and Yallow & Berson (1960) have, in fact, independently developed such a technique although they appear not to have generalized it. More recently Barakat & Ekins (1961) have adopted the principle to the assay of vitamin B_{12} with remarkable success. It is probable that further examples will be forthcoming in the future.

Acknowledgments: I am indebted to my colleagues at The Middlesex Hospital for the whole of the material here presented, particularly to Mr R P Ekins for allowing me to use his diagrams and to summarize his work before he himself has published more than a fraction of it.

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Professor D W Smithers (London) spoke on Treatment; his talk was illustrated by slides.

Section of Anæsthetics

President R F Woolmer VRD FFA RCS

Meeting April 7 1961

Discussion on Patient-triggered Ventilators

Dr D Campbell (Glasgow)

The Case for Triggered Ventilators

Interest was first shown in mechanical ventilators designed to assist a patient's own respiratory efforts by Donald & Young in 1952. A study of the effect of augmented respiration in neonates was reported in 1953 by Donald & Lord. The term 'augmented respiration', or preferably 'augmented ventilation', seems a happy one to describe this technique. Anæsthetists are aware of certain advantages in preserving spontaneous respiration, particularly in anaesthesia for the emphysematous patient. If this can be effected, difficulty in re-establishing adequate alveolar ventilation at the end of an operation, may be avoided. This technique has never been widely used as it is difficult to perform manually.

Nevertheless, the search has continued for a suitable ventilator capable of carrying out such assistance to respiration. However, the real need has probably not been for yet another ventilator but rather for a more sensitive receptor or 'trigger' mechanism, to detect small efforts at spontaneous respiration and signal quickly to the ventilator to start inflation. A ventilator employing such a trigger has been used for most of the observations which follow. This apparatus is the latest of a series developed from the original described by Donald & Young (1952) and details of its mechanism have been reported elsewhere (Campbell & Duggan 1960).

A number of other 'triggered' ventilators have been developed, capable, with intelligent use, of successfully performing this technique of augmented ventilation. For some time, however, their value has been the subject of controversy and the purpose of this paper is to demonstrate that physiological advantages are to be gained from their use.

Comparative Effects of Intermittent Positive Pressure Ventilation and Augmented Ventilation

Methods: The usual techniques of pneumotachography and oesophageal manometry have been employed. A grid-type flow meter has been used for flow measurement, the electrical output of which can be integrated to produce the tidal volume excursions if required. For airway and oesophageal pressure recordings, a differential pressure transducer and electromanometer have been used. Oesophageal pressures have been measured with an open-ended, or ballooned, polyethylene tube of standard length. The actual method used is that described by Opie *et al.* (1959).

When a decision has been made to employ intermittent positive pressure ventilation, in a particular case, it is essential to bear in mind any undesirable effects that may result from this form of treatment.

The cardiovascular system: The potentially harmful effects of intermittent positive pressure ventilation on the cardiovascular system are two: (1) An increase in resistance to pulmonary blood flow. (2) Obstruction of central venous return to the heart.

The pulmonary capillary pressure is approximately 12 cm of water but airway pressures of only half this value can interfere with the pulmonary circulation and throw a burden on the right ventricle (Edwards 1951). This factor assumes great importance in patients on the verge of right heart failure. In order to minimize this effect, it would seem desirable to limit the duration of positive pressure in the lungs, as far as is practicable. This can be achieved if the highest safe inflation pressures are used, thus permitting the required volume of fresh gases to enter the lungs, in the shortest time.

The venous return to the right heart depends on a positive pressure gradient between the peripheral veins and the great thoracic veins and right atrium. Controlled ventilation, by intermittent positive pressure or in a tank-type respirator, causes reversal of this gradient and

impedes the venous return (Crampton-Smith & Spalding 1959). The degree of obstruction is related to the intrathoracic pressure, which is that pressure exerted on the greater thoracic veins and the right atrium. It is not practicable to measure this directly but a reasonable approximation is obtained by measuring the pressure in the oesophagus at the level of the atrium (Howell & Peckett 1957). The mean oesophageal pressure is used as an index of the degree of obstruction to the central venous return. Although positive during controlled ventilation, it can be significantly reduced if negative pressure is applied to the airway, during the expiratory phase. A similar reduction has been observed when augmented ventilation is used (Fig. 1, Table 1). On occasion, when augmented ventilation is carried out with a patient-triggered ventilator, both these effects can be exploited, i.e. the reduction in mean oesophageal pressure, produced in augmented ventilation, with the reduction obtained by applying a negative phase to the airway during expiration.

These findings show that augmented ventilation interferes less with venous return to the heart than controlled ventilation, without a negative phase. Although of little importance in the patient with a stable cardiovascular system, this benefit of augmented ventilation should be valuable in those with some degree of pre-existing right heart failure, especially if the

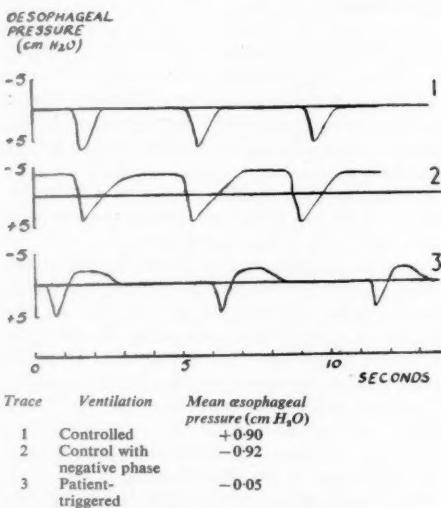


Fig 1 Oesophageal pressure tracings taken during intermittent positive pressure ventilation (1), intermittent positive pressure ventilation with a negative phase (2), and augmented ventilation (3). In tracings (2) and (3) the positive pressure swing becomes smaller and the mean pressure becomes slightly negative

Table 1

Mean oesophageal pressure changes during intermittent positive pressure ventilation (controlled), augmented ventilation and intermittent positive pressure ventilation + [negative phase of -5 cm H₂O (controlled + negative)]

Case No.	Tidal Volume ml	Controlled	Augmented	Controlled + Negative phase
1	320	+1.2	-0.05	
2	350	+0.9	-0.05	-0.9
3	300	+2.0		-1.8
4	350	+0.7	+0.07	
5	300	+0.4	-0.10	-0.6

application of negative pressure is contraindicated, as, for example, in emphysematous subjects.

A limited number of observations have been made on changes in peripheral blood flow with the two types of ventilation. These indicate an increase of approximately 30% in peak blood flow when augmented ventilation is used following a period of controlled ventilation. This finding tends to confirm that augmented ventilation interferes to a lesser degree with the circulation.

The following case demonstrates some of these effects on the cardiovascular system during resuscitation.

Case 1 This cachectic woman, aged 54, with marked emphysema and early right heart failure, had surgery for a pelvic malignancy. A pelvic perfusion with a cytotoxic agent was carried out, the whole procedure taking 7½ hours' anaesthetic time. She developed respiratory failure and became comatosed a few hours post-operatively, at which time arterial blood gas analysis showed an oxygen saturation of 98%, pH of 7.3, carbon dioxide tension of 66 mm Hg and a standard bicarbonate of 21 mEq/l. A tracheostomy, combined with an intravenous infusion of nikethamide and aminophylline, failed to improve her condition and the respirations were controlled with a ventilator. The patient was treated with intermittent positive pressure ventilation for about 2½ hours with no improvement. Following a change to augmented ventilation, with a patient-triggered machine, there was a dramatic improvement in her cardiovascular state and she regained consciousness. No alteration in the treatment took place during this time, other than the change in the method of ventilation (Fig 2). Arterial blood gas analysis now showed an oxygen saturation of 96%, a pH of 7.46, a carbon dioxide tension of 39 mm Hg and a standard bicarbonate of 26 mEq/l.

Effects of the Two Methods of Ventilation on Lung Function

Prolonged controlled ventilation is known to result in a decrease in lung compliance (Butler & Smith 1957). Nunn (1957) suggests that this is caused by an abnormal pattern of inflation. This decrease means that higher inflation pressures, or a longer inflation period, will be required to

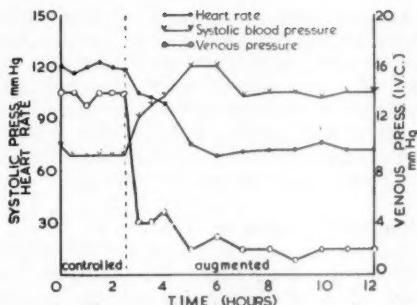


Fig 2 Systolic blood pressure, venous pressure (at the level of the inferior vena cava) and heart rate changes, in a patient treated with intermittent positive pressure ventilation followed by augmented ventilation, on a patient-triggered machine. Note the resultant fall in venous pressure accompanied by improvement in the blood pressure and heart rate

maintain the same level of ventilation. The former is undesirable as the maximum safe pressure should already be in use and the harmful effect of the latter on the cardiovascular system has already been discussed.

Compliance measurements have been made wherever possible, during augmented ventilation and intermittent positive pressure ventilation, in our patients, and a gradual reduction in compliance over prolonged periods has been observed. No significant difference has been noted in this respect between the two types of ventilation.

No difference has been noted in the total resistance to gas flow during the inspiratory phase between the two methods. During expiration, however, resistance is greater with augmented ventilation than with controlled (Fig 3). A possible explanation for this is the continuing tone in the muscles of inspiration during the early part of expiration (Campbell 1958). This is to be expected, since these muscles are relaxed in the controlled patient but retain some activity in patients whose respiratory efforts are being assisted.

The management of patients with low lung compliance who require mechanical ventilation can be difficult. Comroe *et al.* (1955) describe a case where the compliance was reduced to 0.025 l./cm H₂O (1/5 of normal) and where controlled ventilation was inadequate, even when the maximum stroke volume or the maximum inflation pressure of the ventilator was used. The description of a similar case follows, where the lung compliance was reduced to 0.01 l./cm H₂O (1/10 of normal):

Case 2 Female, aged 27.

This patient developed respiratory failure post-operatively, following the repair of an atrial septal defect under hypothermia. An acute fibrinolytic process

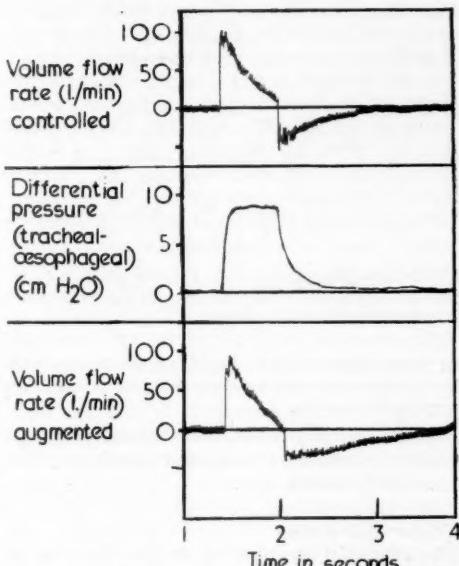


Fig 3 The difference in flow pattern, consistently found in the two methods of ventilation. The tracings were made at the same differential pressure but at different times. During augmented ventilation, the negative flow in passive expiration lasts longer

developed with interstitial, intra-alveolar and intrapleural haemorrhage which resisted all treatment. This patient proved to be an extremely difficult problem when intermittent positive pressure ventilation was employed. Augmented ventilation was then carried out for seven days, with a patient-triggered machine, before she finally died. At post-mortem severe lung damage, resulting from the fibrinolytic process, was demonstrated.

Maintenance of acceptable blood gas levels: Augmented ventilation has been criticized on the grounds that it is difficult to maintain the oxygen saturation, pH and carbon dioxide tension within reasonable limits, without controlling the patient's respirations. Provided a suitable patient-triggered ventilator is used, these levels can be maintained within acceptable limits. In the majority of cases, the stroke volume having been set to something near the predicted normal, the ventilator adjusts continuously to the patient's requirements. That is, during augmented ventilation, the patient, to a large extent, controls the ventilator.

Case 3 This woman, aged 30, had an exploratory bilateral thoracotomy for a possible congenital cardiac defect and was found to have a myocardopathy of unknown origin. She developed respiratory failure, with coma, post-operatively. Despite a tracheostomy, she required augmented ventilation for a period of

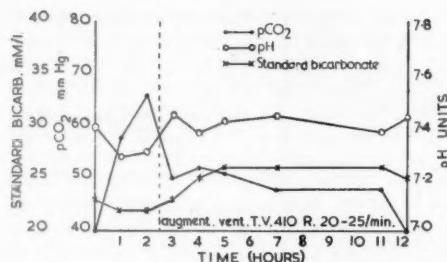


Fig 4 Arterial blood gas values during prolonged augmented ventilation. The patient's initial respiratory acidosis was successfully corrected

about nine hours (Fig 4). Weaning from the ventilator was readily accomplished and the patient made an uneventful recovery.

The ease with which most patients can be 'weaned', even after prolonged ventilation, is a feature of this technique.

Trigger Unit Design

The successful exploitation of the physiological advantages of augmented ventilation, depends on the fulfilment of certain requirements in the design of the trigger unit and ventilator. These are: (1) A high 'trigger' sensitivity. (2) A rapid response to the patient's respiratory efforts. (3) The ability of the ventilator to supply relatively high inflation pressures in a short space of time. The prototype ventilator employed in this investigation fulfils these requirements, using a flow sensitive photo-trigger mechanism rather than the more usual pressure-sensitive type (Figs 5 & 6).

Although the above-mentioned features are important, they are not the only ones influencing the choice of patient-triggered ventilator. In practice, the ability to change the inflating pressures and volumes easily may be important

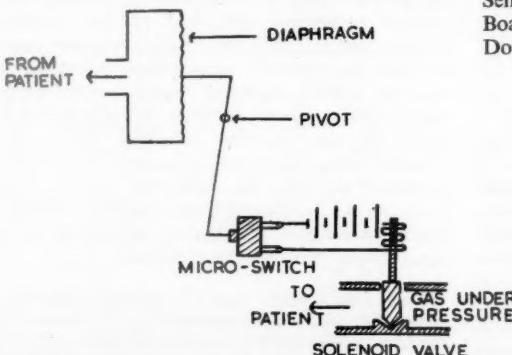


Fig 5 Pressure-sensitive trigger, which operates with a small pressure change and a negligible gas-flow

in the successful management of a particular patient. During this investigation, on more than one occasion, ventilators employing the two types of trigger were directly compared. This demonstrated that augmented ventilation could be maintained readily, with the flow-sensitive trigger, where the patient's efforts were inadequate to operate a pressure-sensitive trigger.

Indications for Augmented Ventilation

In our opinion, the following are the clinical problems in which augmented ventilation has some advantages over intermittent positive pressure ventilation:

- (1) Post-operative respiratory failure, where intermittent positive pressure ventilation with sedation, hyperventilation or curarization is undesirable.
- (2) Certain medical conditions complicated by respiratory failure, particularly in patients with gross hypertrophic pulmonary emphysema, accompanied by right heart failure. Here the application of a negative phase is of no value and may be dangerous, and sedation or curarization is contraindicated.
- (3) Atelectasis neonatorum.
- (4) Where prolonged ventilation has been required and 'weaning' from a non-triggered ventilator proved difficult.
- (5) Possibly as an alternative method of ventilation, during anaesthesia, in patients with poor lung function.

This project is supported by the University of Glasgow and the Scottish Hospitals Endowment Research Trust. I am indebted to Mr T C Duggan, Senior Physicist, Western Regional Hospital Board, Physics Department, to Professor Ian Donald, Department of Obstetrics and Gynaecology.

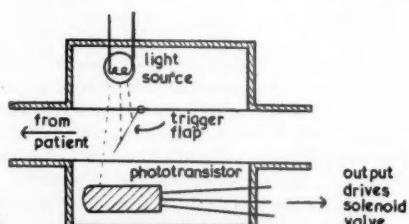


Fig 6 Flow-sensitive trigger, which operates with a negligible pressure change and a small instantaneous gas flow. This flow need only persist for very short periods of time

cology, Glasgow University, and to Dr Alex C Forrester, Reader in Anæsthetics at Glasgow University.

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Dr R Atwood Beaver (London)

The problem concerns the spontaneously breathing but inadequately ventilated patient, in whom, because of the retention of some muscular power, synchronization with an automatically cycled machine is difficult. There are two groups of impairment of respiration: (1) Those due to neuromuscular disease, e.g. encephalitis, brain injury, the muscular paralyses, myasthenia. (2) Those due to mechanical difficulties of ventilation, e.g. crush injuries, post-operative chest conditions, emphysema, cor pulmonale.

Tracheostomy, preferably through a transverse incision, should be performed first, with endotracheal intubation to improve the airway and reduce the dead space, and to permit (with adequate humidification) easy removal of secretions and active physiotherapy. Antispasmodics (such as aminophylline) to reduce spasm and repeated nikethamide injections to stimulate respiration may be valuable. If respirations are still inadequate, mechanical aid to respiration must be employed, either by controlled respiration or by means of a patient-triggered respirator.

Comparison of methods: Psychological and other complications make comparison difficult, and the physiological disadvantages of controlled respiration can be over-emphasized:

(a) *Interference with pulmonary capillary flow:* Inspiratory pressure of over 7 cm H₂O decreases the pulmonary blood flow, but an inspiratory/expiratory ratio of 1/1.5 reduces this to a minimum (Edwards 1957); however, there is a vast difference between 'manometer' and alveolar pressures, and there is no evidence that right ventricular hypertrophy occurs even after months of controlled respiration.

(b) *Absence of the 'thoracic pump':* If blood volume is adequate, the raised peripheral venous pressure probably maintains the pressure gradient even without a negative phase (Brecker 1956).

These factors are of little importance in the vast majority of patients. Although there is a short period of inspiratory negative pressure, and psychologically there is less resentment (in the nervous patient) to a triggered machine, adequate sedation (with pethidine, Largactil and paraldehyde – and more recently R 1406, phenoperidine) has proved satisfactory, and can be pushed to the point of respiratory arrest if the condition is painful, e.g. in chest injury, and after surgery, provided ventilation is adequate. Often, even if the patient still fights the machine, provided ventilation is satisfactory and anoxæmia is corrected the patient will 'follow' the machine. Volume-cycled are better than pressure-cycled machines, which tend to be erratic in this context, and careful adjustment is necessary to avoid an 'explosive' type of inspiratory phase. Setting the expiratory valve at the maximum desired pressure helps to produce a mixed 'volume-pressure' cycling which suits the patient (Beaver 1953).

If respiration is still difficult, a *muscle relaxant* may have to be given. Gallamine in an intravenous drip is less liable to produce hypotension or reduced cardiac output than curare or scoline. The benefits of moderate hyperventilation can now be employed – the rise in pH causes a diminished cerebral circulation and activity, produces sedation, and no harm has resulted from a pCO₂ as low as 25 mm Hg.

Difficulty with 'weaning' is the result of trying to remove the artificial assistance too quickly.

With the *patient-triggered machine*, unfortunately, hyperpnoea may persist (with reduced ventilation), there is a lag between the patient's inspiration and the delivery of air which can distress the patient, and there is increased resistance in the expiratory phase. Hence there may be less ventilation and more struggling than with controlled respiration.

A triggered machine should have the following characteristics: (1) A maximum signal depression of 0.5 cm H₂O or flow sensitivity of 5–10 cc. (2) A minimal delay in air delivery – not more than 0.2 sec. (3) An open passage for inspiration should triggering not occur; in all respects it should 'fail safe'. (4) An automatic delivery of air after a selected interval – say 6 seconds – should no signal be obtained. (5) Provision for adequate humidification.

There are three main categories of machine (Mushin & Rendell-Baker 1959):

(1) Those driven by *compressed gas*. These comprise the majority and the principle is sound in that with the short inspiratory interval available, there is little time for pumping. A separate compressor can be used with some loss of reliability. Also, room air may be entrained via a Venturi, for economy.

(2) Those requiring both *air and electricity*. This seems an unfortunate complication and certainly diminishes reliability. They are easy to produce, and simple diaphragm micro-switch transducers can supply the signal.

(3) The *purely electric machine*. So far as we know only one such exists and has proved utterly reliable over many years. An electric motor is caused to stop and reverse by a system of relays at each stroke (Beaver & Byford 1954). Stopped ready for the pressure stroke, it is triggered by the usual diaphragm. There is undesirable inertia in the bellows, but this failing is shared by two other famous machines - the Blease and American Jefferson.

Possibly all these machines give an inadequate performance, and it is this rather than the principle involved which causes anxiety.

For the moment, we prefer to impose controlled respiration. But there is always the quite exceptional case where, because of insuperable difficulties, one must use a triggered machine.

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Dr A B Kinnier Wilson (London) in describing the B.O.C. 'Cyclator' Type P, said that this machine had several advantages. A single large cylinder would power it for over thirty hours. It failed safe. Only one form of prime mover was required, cylinder gas or a pump. When the trigger was operated, approximately the same tidal volume was delivered per breath. This meant that increasing the respiratory rate increased the minute volume and the alveolar ventilation; this was the point that he wished specifically to emphasize. He had the privilege of trying the Barnet respirator a year ago and found that as supplied to him then the machine acted as a minute volume divider. It did not increase minute volume if the respiration rate increased. Thus the patient's call for more ventilation by increasing the rate of triggering would, in fact, lower the alveolar ventilation.

This point should be considered in all patient-triggered machines. It was no use relying on the patient's respiratory centre for ventilatory control if the machine provided did not respond in a physiological manner.

Professor W W Mushin (Cardiff) said that some confusion still existed about the interpretation of the manometer reading on the ventilator. The pressure, indicated on the manometer on the ventilator, was virtually the pressure

at the patient's mouth, but was not that in his alveoli. Some difference must exist between these two or gas would not flow from one to the other. For a brief instant between inspiration and expiration gas flow between mouth and alveoli ceased. At that instant the pressure was the same throughout the respiratory tract, but the manometer could only indicate this pressure if the arrest of flow was maintained long enough for the manometer needle to settle. In clinical circumstances the arrest of flow was normally far too brief, and it was therefore usually impossible to determine the peak alveolar pressure from the manometer on the ventilator. A very considerable difference of pressure might exist between the mouth and alveoli during inspiration and the magnitude of this difference depended on the degree of any obstruction in the airway, and on the time during which a given tidal volume was to be transferred to the lungs. The pressure at the mouth might reach a peak considerably higher than the final pressure in the lungs at the end of inspiration. A pressure at the mouth of 30–40 cm H₂O was common during manual ventilation. Automatic ventilators should therefore be capable of producing a pressure at the mouth of at least 30–35 cm H₂O if adequate ventilation was to be ensured in patients in whom either the airway resistance was raised or the compliance of the lungs was low. To confuse the pressure on the ventilator manometer (i.e. at the patient's mouth) and the alveolar pressure was a fundamental error, the common result of which was underventilation of the patient. The only sure way of preventing this was to measure the ventilation of the patient with a volume meter, and not to rely on pressure readings at the ventilator.

Dr Alan Gilston (London) asked Dr Campbell whether he had found that adequate alveolar ventilation could be achieved with his (triggered) respirator when the patient had a respiratory rate of 40 or more.

Dr W W Mapleson (Cardiff) referred to Dr Campbell's statement that since his trigger mechanism was flow sensitive it could not be compared with a pressure-sensitive trigger. He pointed out, however, that even with Dr Campbell's trigger the patient would have to produce some negative pressure in order to generate the required flow; and similarly, with a pressure-sensitive trigger mechanism the patient would have to draw some flow of gas, or to displace some volume, in order to develop the triggering pressure. In fact, therefore, it should be possible to compare different types of triggering mechanisms. For example: if Dr Campbell's

mechanism required a flow of 3 l./min for 0·14 sec this represented a volume displacement of 7 ml; while the pressure-sensitive trigger on the B.O.C. 'Cyclator' required a displacement of 5–8 ml and a pressure of –1 cm H₂O. Therefore both mechanisms required about the same volume displacement and if Dr Campbell's mechanism needed a smaller pressure than –1 cm H₂O it would indeed be more sensitive than that on the Cyclator.

Dr J Montgomerie (Bath) said that controlled respiration had for many years been used to indicate the ventilation of a completely apnoeic patient. The use of techniques and apparatus designed for that purpose on a patient attempting respiration was well known to be incorrect. To avoid confusion in teaching he hoped that no change would be made in the exact use of the word *controlled* and that other terms would be applied to conditions where some respiratory effort, however slight, was being made.

Dr D Campbell replying to Dr Kinnier Wilson said that his point that patient triggered ventilators must function in a physiological manner if they were to be relied upon to respond to the

demands of the patient's respiratory centre was important. It was worth emphasizing that the machine used in their investigations and described previously in the literature, as already noted, fulfilled the necessary criteria. An increase in the respiratory rate produced a real increase in the minute volume and the alveolar ventilation. At high respiratory rates (e.g. 40 or more) the machine faithfully followed the patient's efforts until the arterial pCO₂ fell to within the patient's normal range, when the respiratory rate was usually considerably reduced.

In reply to Dr Mapleson he agreed that it was correct that it was theoretically possible to measure the negative pressure generated during the operation of the flow-sensitive type of trigger. This had proved technically difficult in practice, but it is in the region of –0·25 to –0·5 cm H₂O. The trigger unit was sensitive enough to respond to the tiny efforts of neonates under treatment for atelectasis neonatorum.

In conclusion, Dr Campbell said that he felt that augmented ventilation with a satisfactory patient triggered machine was a useful method of treatment in the small group of patients where controlled ventilation by the more conventional methods was contraindicated or unsatisfactory for any reason.

Registrars' Prize Essay

The Management of Patients in a Respiratory Unit [Summary]

by R S Walsh BM (London)

It is now realized that respiratory care is necessary in a variety of illnesses, diseases which are often neurological in origin and in which respiratory failure is a transient but potentially lethal episode. If this phase of the illness can be passed, recovery is often complete.

A respiratory unit was opened in Southampton in 1958 to help in the management of such patients, especially those with tetanus but also those with other respiratory illnesses. Experience has shown the advantages of sending such patients into a central unit—the greater experience of the medical staff, the availability of trained nurses and the accessibility of respiratory and laboratory equipment. It is important that an anæsthetist should accompany patients on the journey from their homes or other hospitals, taking with him all the equipment necessary for respiratory care.

On arrival at the unit the diagnosis has to be confirmed, and decisions taken about the need for tracheostomy and intermittent positive

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pressure respiration (I.P.P.R.), and for any specific therapy for the disease, for example chlorpromazine sedation for tetanus, antagonists for intoxications or corticoids for polyneuritis.

Tracheostomy should usually be performed early, for in competent hands under general anaesthesia it is a relatively minor procedure, and the advantages it has of securing the airway, of preventing soiling of the tracheobronchial tract and of permitting tracheal suction and I.P.P.R. (if required) are outstanding for a patient who is in, or is approaching, respiratory failure. A cuffed rubber tracheostomy tube is used, and care is taken not to over-inflate the cuff.

Humidification is necessary in the early weeks: if I.P.P.R. is used a hot water tank in the breathing circuit is effective. If breathing is spontaneous a low-pressure fan blows air over the surface of the tank. This humidified air then flows through wide-bore tubing to the tracheostomy where it is breathed on a 'T-piece' principle.

The following criteria are adopted for instituting I.P.P.R. in respiratory illness: If there are signs of hypoxia or carbon-dioxide retention, if the respiratory volume falls below proper levels, or if laboratory investigations point to respiratory insufficiency. In tetanus there are two other

factors: When sedation alone cannot prevent muscle spasms sufficiently severe to interfere with nursing, or causing pain; and when sedation has to be so deep as to depress respiration. If muscle relaxation is required *d*-tubocurarine is used and is given intramuscularly after the initial dose.

Mechanical ventilation has usually been provided by Radcliffe pumps, positive-pressure pumps with mechanically operated valves. They have given reliable service and a negative-phase respirator has seldom been required.

The control of I.P.P.R. is based on clinical observation of the patient's condition, helped by measuring the respiratory volume. In cases of doubt it is helpful but not essential to have reliable and rapid laboratory facilities for estimating arterial blood pH and pCO_2 .

Frequent chest radiography is unnecessary. Any atelectasis which it might show should be detected clinically, and remedied, in a shorter time than it takes to order an X-ray.

During drug-induced paralysis it may be desirable to sedate a patient on I.P.P.R., but experience at Southampton confirms the findings of other workers that only the lightest sedation, and sometimes none at all, is required to maintain unconsciousness and amnesia. This may be related to overventilation, but the phenomenon is not seen when the muscle weakness is the result of the disease process itself, and such patients are usually awake.

The weaning of a patient from respiratory care may be prolonged. The transition from cuffed tracheostomy tube to normal breathing is made via the intermediate stage of a fenestrated metal tube, to reintroduce gradually the natural dead-space.

Good nursing is the basis of respiratory unit care. With special training and an adequate number of nurses it is satisfactory to leave all the immediate care to them, including supervision of respirators, giving of curare, tracheobronchial toilet and elementary physiotherapy. Great care is needed in aseptic handling of tracheal suction.

The co-operation of the physiotherapist is needed for care of the chest, and for the limbs, because these patients often waste quickly and develop contractures if not carefully treated.

The nutrition of unconscious patients and those who cannot swallow is provided by emulsified 'Complan' via a plastic naso-gastric tube. The metabolism may be disturbed and nitrogen retention can be observed in tetanus and other respiratory diseases. This is probably related to the wasting of muscles and the breakdown of tissue protein but other causes may be operative. Hyperpyrexia is occasionally met in the neurological diseases needing respiratory care, but it is controllable by chlorpromazine and surface cooling.

Chest infection is made more likely by the patient's immobility and the presence of a tracheostomy, but the isolation of pathogenic organisms from the tracheostomy or the tracheal aspirate is not necessarily followed by frank clinical infection. Prophylactic chemotherapy is always given in the early stages.

The cornea and conjunctiva of the unconscious patient need protection and the use of 10% sulphonacetamide has prevented infection.

I am indebted to Dr R. P. W. Shackleton for his encouragement and advice.

Section of Odontology

President R V Bradlaw CBE FRCS FDS RCS

Meeting March 27 1961

Paper

Safety Precautions in Dental Radiography

by G R Seward MDS FDS RCS MB (London)

The history of radiation protection is well documented. Initially radiographical workers, pursuing their new art with enthusiasm, unwittingly damaged themselves and their patients. As a result of these early experiences it soon became known that exposure to a large dose of X-rays resulted in the appearance of an erythema of the skin or the shedding of hair. Radiographers made use of their hands as test objects during the adjustment of their machines in preparation for a radiographical session. A dermatitis with atrophy, drying and cracking of the skin followed such repeated exposures and eventually neoplastic changes occurred. Filters of sheet aluminium or a piece of old boot leather were interposed in the beam to try to remove the harmful element!

These occurrences led to an awareness of the dangerous nature of ionizing radiations and precautions were taken to limit the exposure of all concerned to safer levels. With improvements in equipment and films, overt damage by diagnostic radiography became a thing of the past and radiographs were widely and freely used. Clinicians were urged to take X-rays for a steadily increasing number of conditions and the lay public adopted the attitude that to omit a radiological examination was negligent.

During and following the Second World War the pace of research into all aspects of radioactivity increased and interest in the effects of ionizing radiations on living organisms was renewed. With the rapidly growing use of radioactive materials in many spheres of activity, increasing concern was felt about the effects of prolonged exposure to minute doses of radiation. This interest resulted in the Prime Minister requesting the Medical Research Council to appoint an independent committee to report on the medical and genetic aspects of nuclear radiations. Their report was published in 1956 as 'The Hazards

to Man of Nuclear and Allied Radiations'. This report focused the attention of diagnostic radiologists on three possible ill-effects from repeated small doses of radiation; the production of mutations in the germinal cells, the induction of leukæmia and the more rapid ageing and earlier death of irradiated persons.

In December 1960 a second report was issued by the Medical Research Council containing further information on these points. Knowledge of the leukæmogenic effects of radiations is still confined to the effect of high doses received in special circumstances. In such cases it now appears that the risk of developing leukæmia following irradiation declines after the lapse of a decade. Unfortunately no evidence has accumulated concerning the cause of the substantial rise in the recorded mortality both of young adults from acute leukæmia and of men from chronic myeloid leukæmia. The possibility that this could be due to chronic exposure to small doses of radiation has been explored, but so far no relationship has been demonstrated between the local incidence of these diseases and the varying level of background radiation or radioactive fall-out. From the new report it now seems that an unusually early death does not follow exposure to repeated small doses of radiations and recent work on mice indicates that the genetic effects of fractional doses given over a period of time are less damaging than a single dose of an equal total value. These are rather less pessimistic views than have been expressed in the past.

When it was first printed, the Medical Research Council report was widely publicized and almost overnight radiography came under a cloud. Medical radiography forms a sizable part of a modern society's experience of radiations and fortunately one over which we have considerable control. A tremendous amount of good has already followed the recent reassessment of radiographical practice. Undoubtedly there is still much complacency to be dispelled, but in doing so we must be careful to keep a sense of proportion.

In reviewing the various measures relating to

radiation dose reduction I will consider the problem under the following headings: Diameter of the primary beam; focus-skin distance; kilovoltage peak and filtration; speed of film; clinical aspects of radiography; technique and the training of operators; gonadal shields; and the X-ray machine.

Many of these factors present a number of facets so that it is not possible to make a short, dogmatic statement about what is right or what is wrong. Experimental investigations are usually designed to test only one variable, so that the resulting reports do not give the answer to the whole problem. I will put forward as many as possible of these conflicting aspects so that one objective may be balanced against another.

The Diameter of the Primary Beam

Ideally the cross-section of the primary beam should be just sufficient to cover the part to be radiographed, or else an unnecessary area of skin and volume of the patient's tissues will be irradiated. The amount of scatter radiations produced is also proportional to the volume of irradiated tissue and if the beam is unnecessarily large, the dose affecting both the patient and the operator will be increased.

Periapical films measure $1\frac{3}{4}$ in. diagonally from corner to corner, occlusal films $3\frac{1}{2}$ in. and for oblique lateral jaw views an area of film of between $3\frac{3}{4}$ in. and $4\frac{1}{4}$ in. diameter is required. Thus the minimum satisfactory beam would be one that would reach these diameters at the varying anode-film distances employed. The most logical way of measuring beam diameter is therefore in the plane of the film. However, the focus-skin distance, which is controlled by the length of the pointer cone, is less variable in dental radiography than the focus-film distance. Hence it is more convenient to discuss the diameter of the beam at the end of the cone.

More than in any other branch, the positioning of the tube in dental radiography depends on the judgment of the radiographer and her sense of spacial relationships. So although a radiographer who has a natural aptitude for the art and is of exceptional skill and experience will be successful with very narrow beams, we would be wise in specifying beam diameters to consider the radiographer of average ability.

It is no use trying to impose laborious procedures which will not be carried out. Equipment for limiting beam size must be simple and must require the minimum of adjustment between exposures. Shutter diaphragms with rectangular apertures are now widely used in general radiography, but similar devices are difficult to use in dentistry where the orientation of the film in

relationship to the tube is constantly altered from view to view. Consequently the conventional, circular beam has practical advantages.

Where an 8 in. focus-cone tip distance is used the skilled radiographer will take periapical radiographs successfully and without coning with a beam only 2 in. in diameter at the cone tip. This will produce a beam of $2\frac{1}{4}$ in. diameter at the plane of the film giving an adequate margin for errors in positioning the tube. But if an occlusal radiograph is taken with such a beam, even though the distance between the skin surface and the film is greater, thus increasing the focus-film distance, the diameter of the beam at the film will be only 3 in. and insufficient to cover it. Obviously a larger focus-skin distance can be used to increase the effective diameter of the beam, but this will increase the exposure time and may well be outside the range of vertical movement of both tube and chair.

If the diameter of the beam at the cone end is increased to $2\frac{1}{2}$ in. it will now be some $3\frac{1}{2}$ in. across at the occlusal plane, an amount just sufficient to cover an occlusal film. A machine equipped with such a cone will also cover an area between $3\frac{1}{2}$ and 4 in. in diameter when used for oblique lateral jaw radiography. Such a machine has been used both for routine radiography and for teaching dental students at the London Hospital for some five years now, and in practice it has been found that only those with a natural eye for the business achieve complete success. Many students and qualified radiographers require a beam $2\frac{1}{2}$ in. in diameter to avoid coning their films.

Thus, where an 8 in. focus-cone tip distance is employed, a beam 2 in. in diameter at the end of the cone will be adequate for periapical and biting radiography in the hands of a skilled dental radiographer. When other views are to be taken the beam diameter must be increased to $2\frac{1}{2}$ in. and where the radiographer is of no more than average skill, to $2\frac{1}{2}$ in.

Two questions come to mind at this point: (1) Why is it worth discussing these small differences in diameter? (2) What can be done to improve the aim of the less skilled operator?

(1) A small increase in the diameter of the beam makes a marked difference to the area which it covers. As Ardran & Crooks (1959) point out; increasing the diameter of the beam from 2 to $2\frac{1}{2}$ in. increases the area irradiated by one-half. If the diameter is increased to 5 in., a size not infrequently used, the area is increased six times. In dental radiography the area irradiated during the taking of one radiograph may overlap that irradiated by the previous exposure and obviously the degree to which this occurs increases with the use of broader beams. With narrower beams there is



Fig 1 A film holder which is designed to facilitate the centring of the tube. The end of the plastic arm indicates the position of the mid-line of the film, but it is bent downwards a little to lie under the cone. The flat end of the cone is aligned parallel to and above the outer edge of the arm. In order to demonstrate the holder the cone has been moved back about 1 in. away from it

less overlap and consequently smaller tissue doses.

(2) Accuracy in centring may be improved either by the use of film holders which guide the radiographer in the positioning of the tube or by some mechanism which indicates the direction of the beam. Provided the patient is co-operative and has a reasonable complement of teeth, the film holder method is successful, but its use proves difficult if only a few teeth remain (Figs 1 & 2). A cylindrical cone, preferably one which is radiopaque, is the simplest way of indicating the size and direction of the beam. Its distal end maps out on the patient's face the area which will be irradiated (Fig 3). For occlusal and oblique lateral jaw radiography a light beam collimator has an application.

If radiopaque cylinders are to be added to existing equipment it is essential that they do not disturb the counterbalance mechanism of the tube suspension. Reich (1953) used lead for his cylinders, but this metal in sufficient thickness to resist distortion during daily use is unduly heavy. Brass cylinders or aluminium cones lined with lead foil have been advocated by Williams, Lysell (1957), Ardran & Crooks (1959) and Manson-Hing (1959). The combination of materials which best provides radiopacity together with lightness and strength is a cone built from a cylinder of Perspex and lined with thick



Fig 2 A film holder for use with the long cone, parallel film technique. The illustration shows how the buccal arm lies parallel to both the film and the buccal side of the tooth. The end of the arm marks the mid-line of the film and enables a narrow beam to be used with success

lead foil. Cylindrical cones are preferable to the pointed variety on other counts in that they limit scatter and reduce the penumbra due to off-focus radiations (Schall 1947, Ardran & Crooks 1959).

The Focus-Skin Distance

For a given degree of blackening of the film, the dose to the tissue is reduced by increasing the focus-skin distance, provided the diameter of the beam is adjusted to cover a similar area. This decrease is due to the filtering effects of the air



Fig 3 A conventional dental X-ray machine fitted with a lead-lined, plastic cylinder of 2½ in. internal diameter. The end of the cone outlines the position of the beam at the skin surface

through which the radiations pass. Some of the softer radiations which previously were absorbed by the tissues are now absorbed by the air and as in any case they do not reach the film, tissue dose is reduced relative to film dose. For example, Ellis (1960, personal communication) has found that if a film is exposed at a depth of 3 cm (1½ in.), then the skin dose is 10% less when a 20 cm (8 in.) focus-skin distance is used than when a 10 cm (4 in.) distance is employed. If the distance is increased to 40 cm (16 in.) the skin dose is reduced by a further 10%.

A second effect of increasing the focus-skin distance is to reduce the degree of divergence of the beam, but again only if its diameter at the film is kept constant.

Increasing the distance will increase the volume of tissue irradiated between the tube and film and decrease the volume beyond the film. As the film is close to the skin the latter effect is the more important. This is modified to some extent by the inclusion of a sheet of lead alloy foil in the film packet, with the object of reducing the effects of back scatter on the film. As Ardran & Crooks (1959) show, in most cases this sheet of foil is very thin. Were it to be thicker it would more markedly attenuate the beam. If the beam then accurately fitted the film some argument might possibly be advanced for using a shorter focus-skin distance. As this is not so, a long focus-skin distance is desirable (Fig 4).

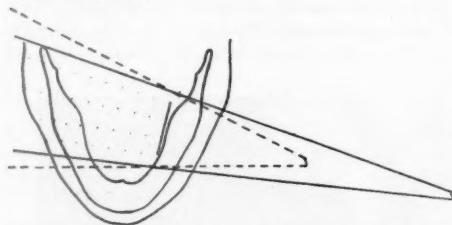


Fig 4 A diagram to show the effect of increasing (continuous line) the focus-skin distance whilst keeping the diameter of the beam constant at the plane of the film. Note how the volume of tissue irradiated beyond the film is reduced. The tissues in the shadow of the lead backing of the film have been shaded with dots. Broken line shows short focus-skin distance

Thus, judged on radiation considerations alone, long focus-skin distances are to be preferred. Unfortunately practical considerations in the design of dental X-ray machines limit the distances that can be employed.

Dental radiography requires a highly mobile tube-head mounted on a fully counterbalanced arm, capable of free horizontal and vertical movements and able to swing over a wide arc. In order to make the equipment electrically safe and to avoid heavy insulated cables, the transformer is

enclosed with the tube in the tube head. This increases the weight of the head and if the suspending arm is to be freely movable, its length has to be limited. The recording of fine detail so necessary for dental work requires a small focal spot of 1 mm square or less which, as the anode is stationary, restricts the output of the machine. The intensity of X-rays decreases as the square of the distance so that increasing the distance rapidly increases the exposure time and if output is limited this can be a serious disadvantage. Both these factors militate against the use of long focus-skin distances.

Recently, by compromising over the size of the focal spot and increasing it to 1.5 mm square, it has been possible to increase the output of dental X-ray machines to 90 kV and 15–20 mA. This gives sufficient power to make longer focus-skin distances practical without excessively long exposures. The tube heads of these machines, however, are very heavy and difficult to suspend without a tendency for them to oscillate after movement. The degree of extension of the tube arms has also been increased to allow for focus-skin distances of up to 16 in. without the need to



Fig 5 A mobile dental X-ray machine capable of 83 kV and 20 mA specially assembled from stock parts of British manufacture. Because of the weight of the tube head the range of horizontal movement is insufficient for long cone technique, unless the patient or the machine is moved. Nevertheless, such a machine has advantages in short exposures and variability of kilovoltage

move the patient, but only pedestal and wall-mounted models can be supplied. These machines have other refinements and are much more expensive than older sets. None of this type is generally available in this country (Fig 5).

Unless it is desired to use the 'long cone' or 'parallel film' technique for periapical radiography, a focus-skin distance of 8 in. would seem to be a reasonable compromise for existing equipment.

Kilovoltage Peak and Filtration

The radiations emanating from an X-ray tube cover a spectrum of wavelengths and the range of the spectrum is proportional to the kilovoltage (kV) applied to the tube. By increasing the kilovoltage peak (kVp) of the alternating current which energizes the tube the spectrum is shifted towards the shorter wavelengths, thus fewer long wavelength rays or rays of low penetration are produced and new, more penetrating ones of shorter wavelength are introduced.

The insertion of a filter of aluminium, copper or some similar substance into the path of the beam attenuates it, but affects the longer wavelength radiations rather than the shorter, so altering their proportion in favour of the more penetrating rays. In contrast to an increase in kilovoltage, however, no new rays of shorter wavelength are introduced and the amount of radiations delivered in unit time is decreased instead of increased (Fig 6).

Both these measures increase the penetration of the X-ray beam so that there are fewer soft radiations which effect skin dose without reaching the film. Consequently skin dose is reduced rela-

tive to film dose. The difference is that increasing the kilovoltage reduces the milliampere-seconds (mAs) of exposure required, providing other factors are kept constant, while increasing the filtration necessitates an increased exposure. Indeed increasing the kilovoltage is one of the most efficient ways of reducing exposure times with dental X-ray machines since for every rise of 10 kV the exposure may be reduced by approximately one-half. Obviously increasing the kilovoltage and decreasing the exposure does not materially affect the dose of radiations reaching the film as the amount of blackening is the same.

There are other factors to be considered. If the penetration of the primary beam is increased, then the penetration of the resulting secondary radiations is also increased, adding to the dose received both locally and generally by the patient and by the operator. Additional scatter radiations will be able to reach the film with an increase in background fogging. Further, with the use of more penetrating beams, the dose delivered to the tissues beyond the film rises in proportion to the film dose and therefore both the thickness of lead foil in the packet and the size of the primary beam assume a greater importance.

Cohen & Stanford (1959), who made measurements at 40, 60 and 100 kV, found the lowest gonadal dose occurred with the use of 60 kV. Unfortunately they do not appear to have done further experiments to determine the optimum value from this point of view. The Adrian Committee 2nd report (1960), speaking generally, says that minimum gonadal doses occurred with the use of 70 kVp with a filtration of 1 mm of aluminium. The minimum skin dose was found with 70 kVp and 2 mm of aluminium total filtration. For dental radiography the conclusion was that the use of higher penetrating powers slightly increased gonad dosage, although they reduced the skin dose (Ellis 1960, personal communication). A contrary state of affairs has been recorded by Richards (1958) who found a reduction in the dose to the male gonads of 11.8% following a change from 65 kV to 90 kV for biting-wing radiography.

Filtration is described in terms of the equivalent thickness of aluminium and is composed of two parts; the inherent filtration of the machine which is contributed by those structures which lie in front of the anode in the tube port and the additional filtration, usually supplied as a sheet of aluminium or aluminium and copper.

Richards (1958) found that the addition of a filter reduced the contrast of the image and this is to be expected since the change favours the shorter wavelength element in the beam. He showed that the optimum total filtration as far as a compromise between contrast and skin dose were con-

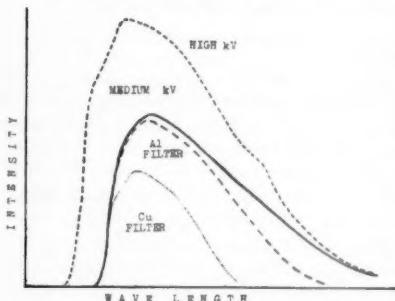


Fig 6 A diagram to show the effects of varying kilovoltage and filtration. Raising the kV produces a beam of shorter peak wavelength, introduces new radiations of shorter wavelength and increases the quantity of rays emitted in unit time. Introducing an aluminium filter into the beam from a medium kV machine removes many long wavelength radiations, produces a beam of shorter peak wavelength, but decreases the amount of radiations emitted in unit time. A copper filter produces a beam of even shorter peak wavelength, but considerably reduces the amount of radiations emitted

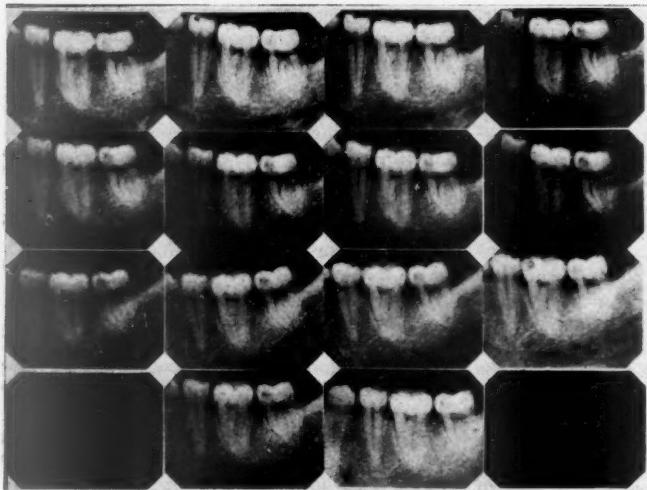


Fig 7 Radiographs of a mandible taken at various kilovoltages. A block of wax has been used to produce scatter similar to that from the soft tissues. All the films are of diagnostic quality, but those in the middle of the series are the most useful. Kilovoltages from right to left and above downwards are: 46, 50, 54, 61 - 66, 71, 77, 83 - 85, 91, 97, 103 - 121, 130

cerned was an amount equivalent to 2.25 mm of aluminium for machines operating between 65 and 90 kV. He noted that the copper and aluminium filter favoured by some authorities reduced contrast below the range of densities which dental films are capable of recording. Such a filter also requires a markedly increased exposure time (Fig 6).

Increasing the kilovoltage likewise affects the quality of the image by increasing the selective penetration of the tissues. Contrast is reduced, but there is an increase in the number of gradations of grey whereby structures are differentiated. A film taken at low kilovoltage is attractive to look at, with structures recorded as near black or near white, but the image contains little detail. Conversely a film made with very high kilovoltage is almost uniformly grey and unless analysed by a log-electronic printing machine is difficult to interpret. The selection of kilovoltage depends partly on the radiographic density of the subject and partly on the visual qualities required by the observer.

Perfectly satisfactory dental radiographs may be made experimentally with tensions between 45 and 130 kVp (Fig 7), but as the kilovoltage is increased the milliampere-seconds of exposure become more critical and great care has to be taken to restrict the diameter of the beam to reduce the fogging effect of scatter radiations. The statement that exposure times may be cut by a half for every rise of 10 kV is most nearly true for kilo-

voltages around 50. If kilovoltages somewhat higher than this are considered the reduction in exposure is found to be less than would be expected. Similarly with lower kilovoltages, the increase in exposure required is found to be greater than expected. These deviations become marked both with very low and very high kilovoltages. The insertion of a filter in the beam introduces further changes in the relationship.

For dental radiographs kilovoltages in the range 60 to 85 are the most acceptable.

Speed of Film

Undoubtedly fast films confer many benefits. With a smaller exposure the level of irradiation at all points is reduced, the life of the tube is prolonged, exposure times are kept short and movement of the patient largely eliminated. Nevertheless all measures which increase speed tend to reduce the quality of the image and once again it is a question of compromise. Unless it is one's habit to radiograph operation and post-mortem specimens on fine-grain, single-coated film one does not realize how much detail is lost in clinical radiographs. All statements on film speed include some reference to an adequate degree of resolution of the image, but it seems that insufficient emphasis has been given to this aspect of the problem in recent years.

To produce a film from which a diagnosis cannot properly be made is to have over-irradiated the patient, however small the dose may have

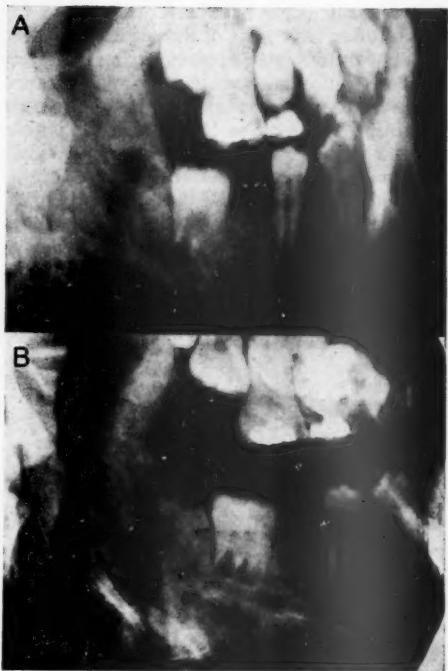


Fig 8 *A, an oblique lateral jaw radiograph taken with medical X-ray equipment and using screen-sensitive film. B, a radiograph of the same patient using a carefully coned beam and non-screen film. The exposure is no more than for a medium-speed periapical film. With the latter technique the small trabeculae of woven bone and the thin cortex are apparent, making a diagnosis of fibrous dysplasia of bone possible. A periapical radiograph with its finer grain would add more certainty to the diagnosis*

been. The object of radiography is to produce films of diagnostic quality, not short exposure times (Fig 8). Thus the fastest film should be chosen which will adequately record the structures which clinical examination suggests will be present.

Clinical Aspects of Radiography

Dental radiographical examinations may either be employed to investigate some definite complaint of the patient, or as a screening test to detect disease which has not yet manifested itself by physical signs or symptoms. A careful history and clinical examination should always precede any radiographical examination. So often one hears that there is not time to take a full history in a busy general practice, but this attitude is difficult to justify. The experienced clinician requires little time to elicit an adequate history from most of his patients. If one presents with some obscure problem it is preferable to say that the matter

requires more lengthy consideration than there is time for at the present visit and to make a further appointment. The dentist should not just 'take an X-ray' for even then he may not reach a diagnosis, or may jump to the wrong conclusion. Not infrequently, a third molar, found in this manner, is blamed without due cause for some obscure complaint!

The clinical examination should include vitality tests where they are appropriate. Too often patients are radiographed when a vitality test is really what is required.

Once the problem has been clearly defined a radiographical examination can be planned intelligently. The views should be carefully chosen, each to serve some definite purpose. Efforts to reduce the dose of radiations to the patient should not lead us to skimp the radiography. An ill-planned, traumatic, inadequate or incomplete operation is likely to do more harm than the completion of a reasonable pre-operative radiographical examination.

There is little controversial about the use of radiography to investigate overt disease, but its use as a screening test is a different matter. Only if the yield is high is such a use justifiable. One can be easily persuaded that one will 'miss' something unless more and more investigations are performed. To my mind only bite-wing radiographs have been shown to have a high enough yield for their routine use to be justified. Many investigators have shown that many interproximal cavities will be missed unless they are taken. In addition the depth of cavities can be gauged with their use, the quality of previous restorations assessed, the crests of the interdental bone can be observed and, in children, the probable presence or absence of adult teeth noted. Few would now challenge their place in the care of patients in general practice.

In the light of our present knowledge, six-monthly examinations are advocated during the periods of maximum caries incidence. It may be that this is based on experience gained in the care of patients at a time when complete reliance was placed on a clinical examination. Possibly the progress of interstitial cavities is slower than is generally believed. This point is important and more research should be undertaken to provide additional information on the rate of appearance and progress of new cavities at various ages so that the frequency of examinations can be better planned than at present.

Technique and the Training of Operators

The general standard of radiography of the teeth and jaws is low. Some of the radiography of the oral structures is very bad. Radiographers are normally taught such dental radiography as they learn either by other general radiographers or by

medical radiologists. Rarely do these teachers have an adequate idea of the scope of modern dental radiography, or of the standard required by the dental surgeon. Senior (1960) has commented on the poor quality of a number of the films submitted to the Dental Estimates Board. Various suggestions can be made to improve matters. Those who instruct radiographical students in dental radiography should themselves have received proper instruction and should be skilled in dental radiography. Proper postgraduate training in dental techniques should be available for qualified radiographers to fit them for posts in the dental radiographical departments of dental schools and hospital dental departments. Such specialized radiographical posts should carry additional pay, so that there is an incentive for radiographers to undertake further training. Refresher courses in dental radiography for general dental practitioners should be encouraged and attention given to the standard of instruction of dental students.

When a patient is referred to another practitioner, or to a hospital for special treatment, it is at present customary to send the radiographs with the referring letter. Obviously where films have already been taken this should be done, but it is probably preferable not to radiograph the patient at all if a transfer is intended. Often the specialist units have their own requirements in the way of radiographical views and prefer to radiograph the patients themselves.

Gonadal Shields

Provided the primary beam is properly restricted and directed and only necessary radiography is undertaken, there would appear to be no need to use elaborate additional precautions. Where the gonads are likely to be in the primary beam they should be suitably protected. Similarly some protection seems appropriate for the trunk, gonads and upper part of the thighs where a great deal of radiography is to be undertaken, especially in small children. Thought should be given to the possibility of an early pregnancy and the foetus protected in all pregnant women.

The X-ray Machine

Dental X-ray machines continue to produce adequate radiographs for many years so that there are still a few antiques giving good service. However, standards of electrical and radiation protection have changed since they were designed and such equipment may well be irradiating both patient and operator to a greater extent than would more modern machines. In the interest of all concerned it is time that these antiques were scrapped and replaced.

The recommendations which have been re-

viewed in this paper have been made before. Indeed so often have some of them been made that it is difficult to quote one authority and not feel that an injustice has been done to many others. We owe it to our patients to see that our present equipment conforms to these standards. If we purchase a new machine then we should satisfy ourselves that it too has been designed in accordance with modern ideas. If this means the rejection of a cheaper machine in favour of one more expensive we should not begrudge the extra cost, if it is to our patients' advantage. Indeed there is a possibility that by concentrating on a small, cheap apparatus, we in this country may fall behind in the design of dental X-ray machines.

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Meeting April 24 1961

Mr Lester R Cahn (*New York*) read a paper on **The Early Detection of Cancer of the Mouth**. This is to be published in the *British Dental Journal*.

Meeting May 29 1961

at the Royal College of Surgeons, London

Following the official business of the Annual General Meeting, held in accordance with tradition at the Royal College of Surgeons, Lincoln's Inn Fields, the Honorary Curator of the Odontological Museum, Professor A E W Miles, gave an account of a demonstration of specimens, illustrating **Growth of the Jaws**, arranged in the newly installed wallcases in the Museum.

The introductory part of the exhibit, which will not be dismantled for several months, gave a brief historical account and illustrated the principal methods by which knowledge concerning growth of the jaws has accumulated. The remainder of the exhibit showed the various changes in the skull that occur from birth to senescence.

Section of the History of Medicine

President K D Keele MD

Meeting May 3 1961

Paper

Robert Watt, Physician and Bibliographer

by A L Goodall MD FRCS (Glasgow)

Robert Watt was an unlucky man. In spite of much effort and erudition in his own specialty of medicine, he has been forgotten by the medical profession. His great claim to lasting remembrance is as the author of the 'Bibliotheca Britannica', probably 'the most stupendous monument existing of the patient labour of a

single man' as Alexander Duncan (1896) so justly describes it. His personal life consisted of a series of tragedies and tragedy continued in his family after his death. It is a work of piety to remember this man who did so much for medicine and for bibliography.

Robert Watt was born in Stewarton, Ayrshire, Scotland, about the beginning of the year 1774. He was baptized in the Parish Church there on May 1, 1774, the Baptismal Register being extant and containing the baptismal dates of his brothers John and David. The Watt family bears several resemblances to the Burns family. Both attempted to cultivate small farms in Ayrshire without sufficient capital to improve the ground and without sufficiently dependable weather to ensure regular valuable crops. The effect of this lack of finance usually was that the farmer was impecunious and that his family had to live the serf's life of a farm servant. Most of these small farmers had little general culture and little education.

Both the Burns family and the Watt family were unusual in that they produced men of genius who were encouraged by their parents to attempt to achieve higher things than the drudgery of small farm life. John Watt held the farm of Bonnyton near Stewarton, now known as Girgenti. He sent his family to school and Robert Watt wrote that 'Among the first things I remember very distinctly was being sent to school about the age, I suppose, of five or six. . . . With two or three masters, I learned to read English, write and count'. He, like Robert Burns, developed a taste for reading and devoured 'Pilgrim's Progress', 'The Lives of Scotch Worthies' and such improving books as he found in his father's house. About the age of 12 Robert Watt left school, possibly due to a deterioration in the family fortunes, and he spent several years in general labouring. During a tour of road building, he was lodged at Ellisland, the farm tenanted by Robert Burns and there he met the poet and used his library. Watt's memories of these meetings were somewhat vague but he was greatly impressed by the genius of the poet.

At the age of 17, Watt went to work with his



Fig 1 Robert Watt. The portrait in the Royal Faculty of Physicians and Surgeons of Glasgow

brother John, a cabinet maker, an arrangement which at first was a great success because he had considerable manual dexterity. Soon, however, repetitive work began to pall and he searched for another interest. At this time, a student of Glasgow University who had befriended his brother John, came down to Stewarton to visit. From him Robert 'received marvellous accounts of what mighty things were to be learned, what wonders to be seen, about a University; and imbibed an unquenchable desire to follow his course'.

Mr Duncan Macfarlane, the schoolmaster at Stewarton, encouraged him by giving him private lessons in Latin and Greek during the year 1792. So successful were these efforts, carried out for an hour each morning before starting work as a carpenter, that Robert was able to enter the classes of Greek and Latin at Glasgow University in 1793. He even won the Greek prize. The following year he studied Greek and Logic and in 1795 he went to Edinburgh University to study Moral and Natural Philosophy. By 1796 he had decided to become a minister and he took classes in divinity. Possibly as a second choice of career or in pursuit of a general education, he enrolled in the class of anatomy and won a prize of £10 for an essay on 'Regeneration'. In 1797/98 he was appointed parish schoolmaster to the village of Symington, near Kilmarnock, and he attended only the class of divinity at Edinburgh in 1797. He won a prize for an essay on 'Prayer'.

About this time he must have had a change of mind for he studied medical subjects thereafter and qualified as a licentiate of the Faculty of Physicians and Surgeons on April 6, 1799. The normal entrance to the Faculty was by apprenticeship and examination but university courses were recognized in lieu of apprenticeship. Watt was asked to discourse on hydrocele and to make up a prescription.

With his new licence obtained he set up practice in Paisley in 1799 and at once began his literary career. His first paper was entitled 'Description of a new instrument for operating for the stone', which describes some improvements to the bistoury caché. His second paper was published in 1800 and was entitled 'Description of a new machine for curing distorted limbs'. These two papers appear presumptuous in view of his lack of experience but they suggest an eager enquiring mind and a man determined to make a mark in his profession. Another small paper in the *Medical and Physical Journal* of May 1801 describes two unusual cases of vaccination.

In 1808 Watt published his first major work, a book entitled 'Cases of Diabetes, Consumption &c., with Observations on the History and Treatment of Disease in General'. It seems naive to-day

and only 1 of the 5 cases described would be accepted as diabetes mellitus. After a review by the *Edinburgh Medical Journal* of this book Watt contributed a paper to that journal.

During his stay in Paisley, Watt married Marion Burns. She appears to have been a local girl and she bore him nine children of whom only one survived her. Several of the others died in infancy and even the surviving child was to die in a lunatic asylum.

In 1807 Robert Watt was elected a full member of the Faculty of Physicians and Surgeons. He was now eligible for office and began to take an active part in Faculty affairs. He served on several committees and particularly on the Library committee. He must at this time have planned to tour England and there is a reference to a paper of his read at Newcastle in 1806 on 'The Manufacture of Dunlop Cheese'. This paper was read by John Chennell in the absence of the author. In 1809 he is also reported to have toured England and in that year he became a member of the London Medical and Chirurgical Society.

In 1810 he became a Doctor of Medicine of Aberdeen University, his sponsors being Robert Cleghorn and Thomas Brown. It may well be that this degree was obtained without examination for the sale of degrees was not uncommon at that time at some Scottish Universities.

About 1810 Watt's ambitions were driving him to look beyond Paisley for fulfilment. He probably considered the possibility of going to England but eventually he set up in a large house in Queen Street, Glasgow, as a consultant physician and teacher of medicine. He was associated with the private school of Alan Burns at which Granville Sharp Pattison also taught. To assist his pupils, and no doubt also to attract new ones, Watt formed a library and in 1812 published a 'Catalogue of medical books for the use of students attending lectures on the principles and practice of medicine'. This rare book begins with a lecture to the students, the rules of the library and a catalogue of 1,066 books ranging from Abercrombius to Zimmermann. There are few subject entries but this evidence of bibliographic interest is of great importance.

In 1813, Watt published his 'Treatise on the History, Nature and Treatment of Chincough'. The most important part of this book is the 'Inquiry into the relative mortality of the principal diseases of children' in which Watt points out the substitution of disease. He noted by laborious investigation of burial registers that, while vaccination had preserved many children's lives, they later died from other diseases such as measles and the total death-rate in children remained much the same. A critical notice of this work in the *Edinburgh Medical Journal* of

January 1814 prompted Watt to reply in a paper entitled 'Observations on the Influence of Vaccination on other Diseases and on Population in General', showing that similar statistics could be collected in all the major towns of Britain.

Watt was now a distinguished citizen of Glasgow, a leading physician and teacher and a man of considerable influence in the medical profession. He became President of the Faculty of Physicians and Surgeons on October 4, 1814. He was a founder member and first president of the Glasgow Medical Society. He was elected physician to the Glasgow Royal Infirmary and he became President of the Philosophical Society.

At the height of his career, fate struck him down. He must have been collecting the materials of the 'Bibliotheca Britannica' for many years before this and 'He saw himself verging towards the afternoon of his life in an impaired state of health and his great work still unfinished. He moved to Campvale and devoted the remaining two years of his life to his Bibliotheca'.¹ Watt died on March 12, 1819, when his great work had just begun to leave the printer's press. He is recorded in the burial register as having died of

¹From the cover of Part I of the 'Bibliotheca Britannica'.

'consumption', no doubt aggravated by the labours which might have been enough for ten men. He is buried in the graveyard of the Cathedral, Glasgow, but by mistake the wrong stone had been placed over his grave.

The 'Bibliotheca Britannica' was dedicated by permission to King George IV and was issued in parts. Eventually, the whole work appeared in four volumes, two of authors and two of subjects. The author volumes gave full references to the works of each and the subject volumes referred back to the authors. The number of authors exceeded 40,000 and not only books but periodical literature were scanned (Fig 2).

There were, of course, mistakes and inaccuracies. Glasgow University, founded in 1451, is stated to be the most ancient institution of that kind in Scotland and to have been founded in 1404.

Watt's politics may be guessed by his reference to the 'illegal and unjust beheading' of Charles I. After all faults and mistakes have been excised, there remains an immense mass of information which was the best available for many years.

The manuscript of the 'Bibliotheca' has had a varied history. After Watt's death it passed to his daughter, Mary, who died in an asylum. The slips

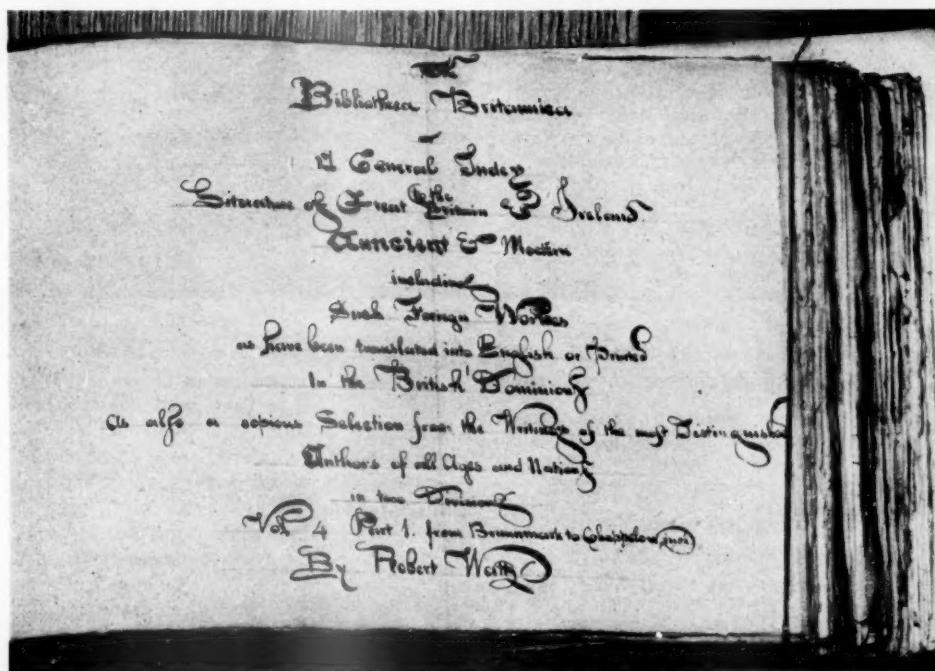


Fig 2 Title page of one of the parts of the MS 'Bibliotheca Britannica'

of paper which composed the work were found in two large sacks and bought by Dr Richmond for Mr Thomas Coats of Paisley. Mr Coats presented these to the Paisley Philosophical Institution, bound in 69 volumes, and in Paisley Public Library they remain.

The last chapter of the Watt family continues to tell of tragedy. Within a few months of Robert Watt's death his house at Campvale was raided by armed ruffians who stole all articles of value from it and even removed the rings from Mrs Watt's fingers. For this crime, four Irishmen were hanged on November 8, 1820.

Mrs Watt was promised £2,000 for the 'Bibliotheca' but the firm of Archd. Constable and Co failed and she received not a penny. This failure also ruined Sir Walter Scott. Watt's two sons died and his daughter, after a disappointment in love, became insane. She died in 1864, a few days before a Government grant was voted for her upkeep.

Thus lived and died Robert Watt, born in lowly obscurity, rising to eminence in the medical profession and finally disappearing from memory, with all his house. But one monument remains, the 'Bibliotheca Britannica', and by this to-day we remember him.

Acknowledgments: My thanks are due to the President and Council of the Royal Faculty of Physicians and Surgeons of Glasgow for permission to reproduce the portrait of Robert Watt and to Mr W E Towler for the photographs.

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Manuscripts of the Treatise on Chincough, Minutes of the Glasgow Medical Society, Minutes of the Faculty of Physicians and Surgeons are preserved in the Royal Faculty Library. Manuscript of the Bibliotheca and Minutes of the Paisley Medical Society are in the Paisley Public Library.

Meeting June 7 1961

The following papers were read:

Anatomical Microslides and Microscopes of the Past Century

Mr F C Grigg (*London*)

Early History of the Microscope in Clinical Practice

Dr W D Foster (*Birmingham*)

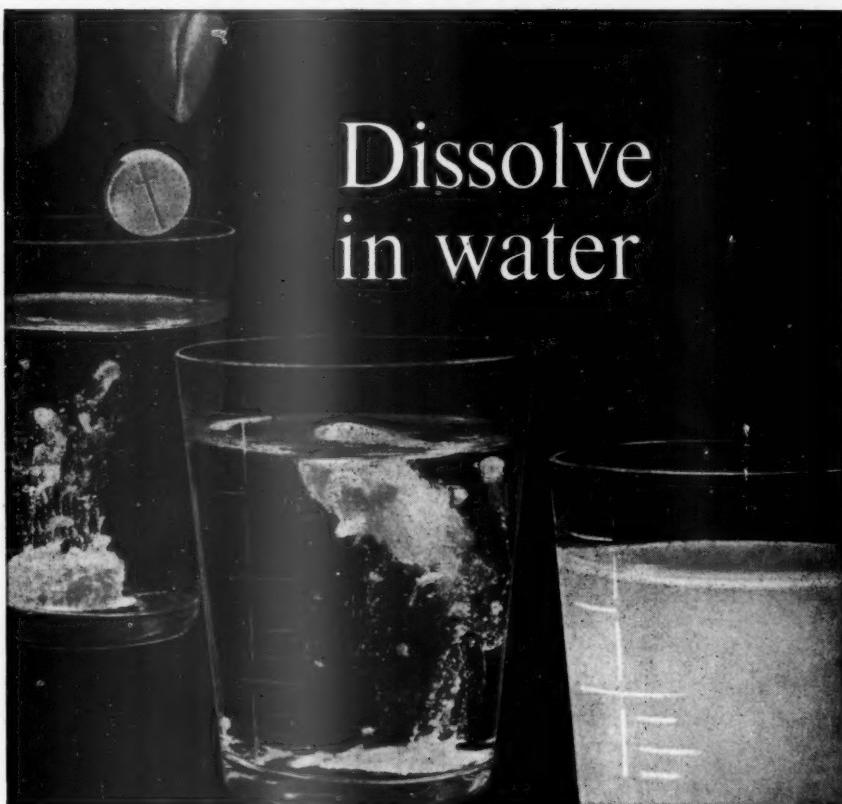
John Hunter's Microscope Slides

Miss Jessie Dobson (*London*)

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Clinical Section

President T C Hunt DM

Meeting March 10 1961

(continued from August 'Proceedings' p 692)

Cases

A Female Case of Hæmophilia

Leo Gilchrist MD MRCP DPM

History: Mrs M H, aged 76, has suffered from frequent and severe epistaxis since childhood and has always bruised easily with prolonged bleeding from trivial injuries. Her periods began at 18, becoming excessive at 25, and after each of her 3 confinements she spent four months in bed because of excessive bleeding. The first pregnancy produced a miscarriage (Fig 1, VI 2), the second her hæmophiliac son (VI 3), and the third a female child (VI 4) who died at 8 months of cerebral haemorrhage. In 1934 Mrs M H was given radium therapy without effect for uterine haemorrhage of unknown cause; her menopause occurred at 55.

Since 1918 she has had repeated melænas (many requiring transfusion) and one haematemesis. In 1932 she bled for four weeks after a dental extraction and had haematuria for which no local cause was found.

Since her late 20s painful swelling of her joints has occurred periodically. The swelling lasts from a few days to weeks and sometimes occurs spontaneously.

On examination: The right hip is deformed with shortening and eversion of the leg. The left wrist,

right elbow and left knee are also deformed with limitation of movement.

Investigations: Blood examination revealed a deficiency of antihaemophilic globulin in the plasma with a normal reaction in the serum, typical of classical hæmophilia. An X-ray of the right hip (March 1960) showed gross osteoarthritis with flattening and deformity of the femoral head. A barium meal showed a duodenal ulcer.

Inheritance: She is the daughter of a first-cousin marriage in a well-known family of bleeders (Fig 1), first described by Treves (1886). The evidence of the inheritance in the first four generations is not typical of hæmophilia, but it is incomplete and unreliable, so they have been disregarded. The patient's father (IV 14) was a hæmophiliac by tradition, and if her mother (IV 11) was a carrier they should have produced (Fig 2) homozygous (XX) or female hæmophiliacs, heterozygous (XX) or carrier females, male hæmophiliacs (XY) and normal males (XY) in approximately equal numbers. Amongst the 12 children of Mrs M H's parents, there were 3 female hæmophiliacs (V 5 – Mrs M H, V 8 and V 12) verified by laboratory examination, while V 10 and V 1 were bleeders by tradition. Two sons (V 4 and V 14) were hæmophiliacs and the third (V 15) was normal. This

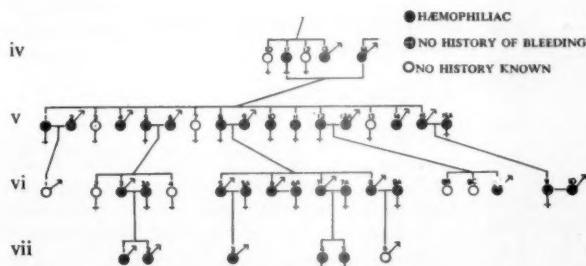


Fig 1 Hæmophilia. The Treves tree

50

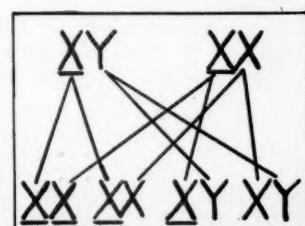


Fig 2 Offspring expected from union of male hæmophiliac (XY) and carrier female (XX). (See text)

leaves only carrier females to be accounted for, and at present a carrier can only be detected if she gives birth to a haemophiliac son. Two of the daughters (V 3 and V 13) died very young. Then there was a female miscarriage (V 7) and a 'normal' sister (V 11) who did not marry. Some or all of these 4 should be carriers (the others being

female haemophiliacs) for the inheritance to be correct.

Mrs M H fulfills the genetic, clinical and laboratory criteria necessary for the diagnosis of haemophilia (Merskey 1951).

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*Meeting May 10 1961
at the Essex County Hospital, Colchester*

Cases

Carcinoma of the Breast in a Male

T A Ogilvie FRCS

S W, male, aged 66

May 1955: Admitted with a lump on the left chest of twelve years' duration. It had started as a small red area near the nipple and had grown slowly and progressively larger. Recently it had become ulcerated and the principal reason for his attendance at hospital was that his wife objected to the smell.

On examination: There was an enormous fungating carcinoma on the left chest approximately 25 cm in diameter and extending from the clavicle to the sixth rib and from the sternum to the mid-axilla. It was firmly fixed to the chest wall but the axillary lymph nodes were not enlarged and there was no evidence of distant spread.

Investigations: X-ray of the lungs and chest wall showed no evidence of pulmonary deposits and no radiological evidence of involvement of ribs or sternum.



Fig 1 Appearance of carcinoma after treatment

Pathology (Dr R D Reid): Tissue obtained by incisional biopsy disclosed polygonal cell trabecular and tubular carcinoma. There was much lipid material in the cells.

Treatment and progress: The patient was initially treated with stilboestrol 60 mg daily but this dose was gradually reduced to 15 mg daily. The tumour began to shrink shortly after therapy was commenced and the ulceration healed. After treatment for seven months the tumour had shrunk to one-quarter of the original size and now formed a flat indurated mass on the chest wall measuring 9 × 10 cm.

Since early in 1956 the tumour has remained unchanged (Fig 1). There is no axillary lymph node involvement and no evidence of distant metastasis. The patient remains fit and well and is in full employment. He continues to take stilboestrol 15 mg daily.

Discussion: This man has now had a carcinoma of the breast for seventeen years. For the past six years it has remained stationary without evidence of spread and the patient and tumour are living in harmony.

No further treatment is contemplated unless this relationship breaks down and the growth begins to spread.

Acute Ulcerative Colitis Presenting with Skin Gangrene

A B Pollard MD MRCP

Mrs M G, aged 53.

History: Admitted to a surgical ward in January 1960 with ulceration and cellulitis of the lower left leg (Fig 1). There was some initial improvement with antibiotics but skin grafting failed. Rapidly spreading gangrene of the skin of the left leg then developed, also bedsores and gangrene of both buttocks.



Fig 1 Appearance of left leg

During February 1960 she gave a history of persistent diarrhoea with blood and mucus which began several weeks before admission.

Examination: Sigmoidoscopy showed acute ulcerative colitis.

Investigations: Hb 40%. W.B.C. 13,000. Blood culture: organism of coliform group isolated. Barium enema (March 1960): substantial ulcerative colitis.

Treatment and progress: She was given blood transfusions, prednisone and tetracycline. Her general condition gradually improved and the diarrhoea subsided.

March 1960: Metastatic abscess developed in left forearm.

April 1960: Skin grafts to left leg and buttocks were successful. Steroids were discontinued and sulphasalazine substituted. Her condition steadily improved and she was mobilized. The colitis was quiescent.

October 1960: Further skin grafting was followed by a relapse of colitis which responded to prednisone and sulphasalazine.

May 1961: Satisfactory progress since last relapse and colitis quiescent.

Summary: A patient with acute ulcerative colitis who presented with extensive skin gangrene of the leg and buttocks. Remission of the colitis followed medical treatment and the skin lesions were then successfully grafted.

Spontaneous Hypoparathyroidism

S A Propert MA FRCP

A G, male, aged 13.

History: A year before admission he first complained of 'pins and needles' in his hands and feet and at that time he had been given calcium em-

pirically with complete relief. He thereafter remained well until a week before his recent admission when his paraesthesiae reappeared. He had no other complaints.

His past history and family history were uninformative but it was noted that he did not like milk.

On examination: An intelligent, well-built child, normal sized for his age. Teeth and nails normal. No cataracts in the eyes; no signs of ectopic calcification. C.N.S.: all reflexes exaggerated but equal on both sides. Plantar responses flexor. Chvostek's and Trousseau's signs positive. Pool's and Schlesinger's signs negative.

Investigations: Serum inorganic phosphate 8 (normal 2.5 to 4.5), calcium 6.4 (normal 9 to 10.5), blood urea 13 mg%.

Serum alkaline phosphatase 38 K.A. units (normal up to 20 units). Serum proteins: total 6.4, albumin 4.5, globulin 1.8 g%; A : G ratio 2.5 : 1.

Hb 103%. W.B.C. 3,500(neutros. 27%; eosinos. 4%, lymphos. 60%, monos. 8%, basos. 1%). E.S.R. (Westergren) 2 mm fall in one hour.

Faecal fat content normal.

Ellsworth-Howard test: the response was in favour of the diagnosis being one of a primary hypoparathyroidism.

Treatment and progress: Following the Ellsworth-Howard test his serum calcium and phosphorus levels returned to normal and he became asymptomatic. He was discharged taking vitamin D, 50,000 units and calcium gluconate 4 g daily.

Pneumatic Drill Injury

R N Jones MCh FRCS

The patient, a man of 35, was first seen in June 1960 and admitted for investigation. He used a pneumatic tool at work and on May 2, 1960, he received a severe jolt when a pneumatic chisel broke. Since then his left hand had felt numb and cold, and its colour had varied between white and blue. He was a trade union official and knew all about Raynaud's disease.

Cyanosis of the hand was not usually evident, but it was observed from time to time by the Ward Sister. There was glove anaesthesia of the hand but no muscle wasting. No evidence of a cervical rib was found.

He was referred to a neurologist who recommended return to work. However, his symptoms became worse and he was readmitted to hospital in April 1961 as the hand was now always cold and cyanotic and felt as if he had 'pins and needles'. An arteriogram revealed a block in the



Fig 1 Arteriogram of left hand

terminal part of the ulnar artery and multiple blocks of digital arteries (Fig 1).

Operation: Left cervical sympathectomy; some compression of the subclavian artery by the scalenus anterior muscle was found.

Progress: Since operation, the hand has been continuously warm, sensation normal and the patient very contented.

The following cases were also shown:

- (1) Klippel-Feil Syndrome
 - (2) Calcification of the Buttocks
- Mr T A Ogilvie

- (1) Renal Tumour with Renal Arteriograms
 - (2) Abdominal Tumour
- Mr R N Jones

Institutional Neurosis - Sixty Years in Hospital
Dr Russell Barton

- (1) Osteogenesis Imperfecta
 - (2) Chronic Osteomyelitis Right Femur. Amyloid Disease
- Mr Denis M Dunn

Carcinoma of the Vulva (Four Cases)
Mr K M Mackenzie

Advanced Carcinoma of the Breast (Bilateral)
Mr Ronald Reid

Fulminating Ulcerative Colitis Treated with Steroids and Antibiotics. Colon Perforation and Peritonitis Treated by Ileostomy. Satisfactory Recovery and Remission
Dr A B Pollard

Bilateral Ureteric Reflux with Hydronephrosis Demonstrated by a Micturating Cystogram in a Girl aged 10 years with Recurrent Pyelonephritis who has a Normal Intravenous Pyelogram
Dr C B M Warren

Addison's Disease in a Hypertensive Subject
Dr S A Propert

Section of Dermatology

President Hugh Gordon MC FRCP

*Meeting March 16 1961
(continued from August 'Proceedings' p 698)*

Cases

Two Cases of Photodermatitis Due to Tetrachlorsalicylanilide (TCSA)

D S Wilkinson MRCP

An outbreak of photodermatitis involving 53 patients has recently been encountered in Buckinghamshire and in workers in a factory in Maidenhead. The following cases are examples of the condition.

Case 1 R B, aged 39, bricklayer.

History: He noticed a tingling sensation of his face and neck in December 1960. This was quickly followed by some redness and swelling of these areas and cracks beneath the ears. The condition subsided temporarily but recurred more dramatically at the end of February with a 'burning' of the neck and face followed by oedema of the eyelids and an erythematous rash. This then affected the backs of the hands and forearms. He had been using a popular germicidal soap. Fig 1 illustrates the condition but is a photograph of another case.

When seen on 28.2.61 he showed a marked erythema and scaling of the light-exposed areas of the face, neck, the 'V' of the chest and the backs of the hands and forearms. There was a little swelling of the eyelids.

The condition gradually subsided until 11.3.61, a Saturday. He had left off using soap but on this bright day walked 2-3 miles to hospital for tests and on return home washed his face and neck. An acute exacerbation took place and when seen the next day he had considerable oedema and scaling of the same areas, which were deeply red in colour. It is likely that he had used the original soap for washing as it was kept in the same dish as a kitchen soap. He was taking 2 tablets of chloroquin a day at the time.

He was admitted to hospital (the seventh such case to be admitted urgently) on 14.3.61 when the condition had already considerably improved.

He shows the following typical features of this



Fig 1

Investigations

Patch-tests:	2.3.61	TCSA 0.1% (alc.)	+++ 72 hours
		Soap solution with TCSA (1%)	+
		Hospital soap (1%)	-
		Soap as now sold (0.5%)	-
		Old type soap (without TCSA)	0.5%-
	14.3.61	TCSA 0.1% (alc.)	++
		TCSA 0.25% (alc.)	++
		(oil)	++

condition: (1) Adult male - outdoor work.
(2) Uses a popular soap containing a germicide.
(3) Fairly acute onset at fine week-end: exacerbation on similar occasions.

Case 2 Mr F C, aged 40, director of radio works.

History: This patient, the 52nd with this condition, was seen for the first time on 15.3.61. In mid-January on a journey to London on a fine day he noticed his face and neck tingling and smarting. It became red and there was some infra-orbital swelling. The ear lobes were affected and a crack developed under the right ear.

The condition settled down in about a week and did not trouble him greatly for the next few weeks. On March 10 a sudden recurrence took place, with redness, swelling and scaling of the face and neck and some erythema on the backs of the wrists. He uses a soap known to contain TCSA (among others) and although normally an indoor worker often makes long car journeys. There is no previous history of skin trouble. He does not suffer from dandruff, nor has he ever suffered from atopic dermatitis or asthma.

He showed a typical picture of some thickening, redness and slight oedema of the face, neck and backs of the wrists, limited exactly to the light-exposed areas. He also shows the typical lichenified appearance of the sides of the neck, which is present in the subacute stage of this condition, and the dryness and cracks around the lobes of the ears.

Investigations: Patch-tests were carried out; a dab of 0.1% TCSA was applied on the right side of the forehead also.

(48 hours) TCSA 0.1% ±
0.25% +
Forehead dab faint positive with itching.

Comment: The history of this rather extraordinary outbreak goes back to the beginning of November 1960. As a full account has been published elsewhere (Wilkinson 1961), I will only describe now the main points about this eruption, which has obviously been seen in many parts of the country. Early in that month I was called to see 2 patients presenting the same picture as Cases 1 and 2; in the next two months 5 further cases were seen. The eruption usually started at the weekend, and the patients were mostly outdoor workers. The rash had all the characteristics of a photodermatitis, but the cause could not be found, despite intensive investigations. Early in January I saw 3 more cases in men who all worked in the same factory. Visits to the factory disclosed many more cases – nearly a third of the workers in one shop were eventually affected. There were several curious features about this outbreak which raised some doubts about its industrial origin. The workers usually reported the eruption on a Monday morning having developed it at the week-

end; and recurrences occurred over the Christmas holiday. Among samples taken for testing was a bar of soap used for washing. This was a well-known brand of toilet soap containing a germicide. Suspicion was aroused when a positive patch-test occurred to a 1% solution (though this may well have been a false positive reaction). A review of earlier hospital cases showed that they had all used this soap or another one with the same germicide incorporated. Since then, another 16 cases have been seen in hospital practice, the most recent one being Case 2.

The manufacturers of the soap confirmed that a new germicide, tetrachlorsalicylanilide, had been present in the soap for a limited period, but that this had been discontinued some months before I approached them. However, supplies would still be held by the wholesalers and retailers.

I should add that the manufacturers have not only been most helpful in giving every assistance, but have gone to the extreme length of organizing the withdrawal of all soaps containing this substance – a very considerable operation.

Tetrachlorsalicylanilide was developed as a germicide and deodorant. A large number of tests were carried out on human subjects without any reaction that would provoke suspicion. It is not, therefore, easy to predict a photosensitizing effect. A full description of this substance is given by Lennon *et al.* (1960). It is possible that it is incorporated at the present time in other cosmetics, particularly deodorants.

The eruption is preceded by tingling and burning and a sensation of discomfort rather than by itching, and is followed by the development of redness and oedema – sometimes quite considerable – of the face, neck and ears, and confined to the exposed areas. This arises with great rapidity and declines rapidly, particularly when patients are admitted to hospital. The course is one of declining erythema, scaling and increasing pigmentation. A peculiar lichenified appearance of the neck, resembling that of atopic dermatitis, often develops.

Biopsy of an affected area showed a dense lymphocytic infiltration, especially around the sweat ducts and blood vessels, but no spongiosis.

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Two Cases of Photodermatitis due to Tetrachlorsalicylanilide

G C Wells FRCP & R R M Harman MRCP

Case 1 A O, male, aged 53, printer.

History: For five weeks an erythematous scaly rash has been present on the face. It began on the chin and spread diffusely over the rest of the face, ears and neck. The eyelids became oedematous so that he could scarcely open his eyes, and there has been intense irritation. Later the backs of the hands and forearms became similarly affected though less severely. He has always used a well-known brand of toilet soap. As a printer he works at night, but at home he gardens with his sleeves rolled up.

Past history: No eczema or dermatitis.

Clinical findings: He shows a diffuse, scaling erythema of the face and neck, with oedema of the eyelids. The scalp is not affected and the rash stops sharply at the collar line. There is also redness and scaling of the backs of the hands and fingers and of the exposed parts of the forearms. No investigations have yet been done. He attended hospital for the first time this morning.

Case 2 J H, male, aged 66, security officer.

History: Since October 1960 this man has had an itching dermatitis of the face, ears, neck and backs of hands. When first seen in December 1960 he was thought to have a seborrhoeic dermatitis. Over the next two months partial recovery was interrupted by acute episodes, leading to widespread exudative dermatitis of the exposed parts. He had always used the same brand of toilet soap.

Past history: No eczema or dermatitis.

Clinical findings: He still shows erythema and scaling of the exposed parts, though areas protected from sunlight are completely spared.

Investigations: Positive patch tests to 1% tetrachlorsalicylanilide in spirit are demonstrated.

Comment: I started to see these cases in October 1960 and I was immediately struck by their uniformity. They all had the appearance of a contact dermatitis of the parts exposed to sunlight, the appearance being similar to some of the chlorpromazine dermatitis we used to see. Two of my patients had used the same brand of toilet soap which I suspected might have caused the trouble, but patch tests only produced the irritant response

usual with soap. Added to this I have seen several men with identical eruptions who had not used this particular soap. I was not able to get any further with this problem until Dr D S Wilkinson told me of his experience, whereupon it became obvious that all these patients were users of another popular toilet soap. It had not occurred to me that a new chemical might have been added to this soap. Through Dr Wilkinson we have been able to get tetrachlorsalicylanilide and to do patch tests on many of these patients. During the past five months I have seen 25 of these cases at St. John's Hospital for Diseases of the Skin, and at St Thomas's Hospital I have seen 8. All were men. Most cases seem to settle down within a few weeks of avoiding the offending soaps, but in some instances exposure to sunlight has produced acute exacerbation several weeks after recovery though still avoiding soap.

Our first patient (Case 1) illustrates the acute phase of this photodermatitis from tetrachlorsalicylanilide and our other patient (Case 2) shows chronic dermatitis from the same cause.

Photodermatitis Due to Tetrachlorsalicylanilide

C D Calnan MRCP

J G, male, aged 47

History: Since October 1960 this patient has suffered from a dermatitis of the face, neck, ears and backs of hands. He has always used a well-known brand of toilet soap. No previous history of eczema.

On examination: Erythematous and oedematous dermatitis of the face, ears and neck, with a sharp margin at the collar line. There has been severe eyelid swelling. The backs of the hands are less severely affected.

Investigations: Patch test to tetrachlorsalicylanilide (1% in methyl ethyl ketone) positive at forty-eight hours.

Comment: It is worth recording that the manufacturers ceased incorporating this substance in their soap before any proven cases of contact dermatitis were reported to them by dermatologists.

The clinical picture is very similar to the photo-contact dermatitis from sulphonamides and chlorpromazine. It shows the same curious anomaly of dermatitis being confined to the light-exposed area, but patch tests being positive on the covered parts. It is true, however, that sometimes the tests are only positive after exposure to light, similar to experience with chlorpromazine.

One may ask if this unfortunate event could have been avoided. If the substance had been submitted for dermatological evaluation, would its dermatitic potential have been discovered before being used in soap by thousands of people? Hind-sight is more readily acquired than foresight.

Dr R R M Harman: Forty-nine cases have been diagnosed clinically at St John's Hospital. These include 17 cases which have been patch-tested to 1% tetrachlorsalicyliide; all except 2 have produced positive results.

Dr J E M Wigley: Have all the cases so far as we know been people who have used soap for the usual purposes or are they concerned in the preparation and manufacture of the soap in any way?

Dr G B Dowling: Do Dr Wilkinson, Dr Wells or Dr Harman know how long this light sensitivity persists? Does it go on for a very long time or can the patient expect to get well within a certain time?

Dr R P Warin: May I ask when this substance was first used in the toilet soap and also do the authors know of any other preparations which now contain it?

Dr W Frain-Bell: I should like to ask Dr Wilkinson how many of his cases produced positive reactions at forty-eight hours as I was not quite clear whether most of them reacted at that time interval or not until ninety-six hours after application of the test? It would also be interesting to know whether any of his subjects were photosensitive, that is to say produced abnormal reactions to sub-erythema doses of ultraviolet light on exposure of their normal non-patch tested skin.

Dr E J Moynahan: Might I ask if this is due to visible light or to ultraviolet light?

Dr H R Vickers: I would like to ask Dr Wilkinson if he has any idea at all of the incidence of this. How many people in the factory were not affected by this toilet soap? Is it possible to know how long the sensitivity period is? We have been particularly looking for this condition in Oxford and we have seen it only in people outside Oxford. There seems to be a definite regional distribution in this condition and it would be interesting to know the experience of people from areas other than the London counties.

Dr J B Lyon: Two years ago, a synthetic detergent-soap toilet product was marketed in Ipswich and Oxford; it very soon had to be withdrawn due to our picking up a number of dermatitis cases. I never got to know what the activating agent was.

Dr E J Moynahan: I think we have to be a little careful otherwise we shall find ourselves denigrating this toilet soap. The lesson to be learned is that manufactured products do not bear a constant formula; manufacturers are apt to introduce things from time to time without proper controls beforehand. We have had an example of that recently where every person patch-tested reacted quite vigorously and some workpeople got a rash before the product was put on the market,

and I think that is happening all the time, new things are being introduced without a proper control. The feature in this case which no one has noticed before is photosensitivity which distinguished it from other contact dermatitis, otherwise it might well have been missed for much longer.

Dr D S Wilkinson (in reply): In my experience all those affected have been users of the soap and not engaged in the manufacture. I do not know how long the light sensitivity lasts, but at the factory the soap was withdrawn on January 18, 1961, and I understand from Dr G Wynne-Jones, the medical officer, who has worked extremely hard on this problem, that he has not seen any major attacks or recurrences since. All the men are working normally. I think that the sensitivity does become markedly less after leaving off the incriminating soap. It is important to check that they really do this, for one of my patients here to-day used it once on a very fine day and had an acute relapse, although I advised the withdrawal of the factory soap in January, the manufacturers had already ceased to incorporate TCSA in the soap in October - several months before I got in contact with them. It had been introduced into the soap in July 1960. Of course there is a considerable time lag as it passes through the hands of the retailers. Although patch-tests are usually positive at forty-eight hours, we have seen some delayed reactions and others that are more marked at seventy-two hours. The factory workers had a dirty job, and used a considerable amount of soap. Moreover, a third of them used the same soap at home - a much higher average than that of the general population, as recorded by questioning nearly 300 consecutive patients at skin clinics. The only 3 men in the factory affected outside the one particular shop all used this soap at home. I do not know of any other product containing TCSA at the moment, but we are naturally investigating other cosmetic and germicidal preparations.

The peak absorption spectrum of TCSA is said to occur at 2957 Å. But many of my patients have suffered flares of the dermatitis through window-glass.

I have no idea of the incidence. Many patients were only referred to the clinic after several months; I imagine a much larger number may have had milder attacks and perhaps changed their soap without doing anything else about it.

Finally, I agree that it is extremely difficult to see how any of us could have condemned this substance on the results of routine patch-testing; normal patients do not produce a positive patch-test even at 1%.

The President: I am sure all Fellows are very grateful for this exposition of this interesting problem. I hope I am not unique in having to confess that I had not heard of it before. If there are others similarly placed they will no doubt agree with me that they can now diagnose at least two or three cases in retrograde who presented with this curious dermatitis on the exposed areas with a tendency to relapse after a week-end.

Section of Orthopaedics

President A L Eyre-Brook MS

Meeting March 7 1961

Cases

Atlanto-axial Subluxation

F J Moynihan FRCS

This case record illustrates the difficulty of diagnosis and the problem presented by failure of its recognition in the early stages.

Case History

W G, girl, aged 11

In August 1959 this girl was coming down a slide when a friend called to her and she jerked her head suddenly to the right and felt a click in her neck. She experienced pain in the neck and right side of her head. Her neck was held stiffly and any walking or jolting gave pain. A diagnosis of 'ricketed neck' was made and she was treated by physiotherapy, traction and manipulation without relief. Immobilization in plaster of Paris relieved the pain but the deformity persisted. She was referred for further advice in December 1960 on account of increasing deformity. At present she has only occasional pain and engages in all sporting activities.

Past history: No febrile illness (relevant to August 1959).

On examination: The patient stands with her head tilted – the right ear towards the right shoulder and the chin directed towards the left. There is marked facial asymmetry (see Fig 1). Movements show full flexion and extension, almost full lateral flexion, but virtually no rotation. There are no abnormal neurological signs.

X-ray examination revealed a right anterior atlanto-axial subluxation. The antero-posterior X-ray (see Fig 2) showed that the right atlanto-axial joint was not visible and that the atlas was tipped down and to the right partly overlying the axis.

An antero-posterior tomogram clearly showed the left atlanto-occipital and atlanto-axial joints and the right atlanto-occipital joint, but it was not possible to visualize the right atlanto-axial joint. The odontoid was displaced to the left.

The lateral X-ray (see Fig 3) revealed marked separation between the odontoid process and the arch of the atlas and superimposition of the axis and atlas.



Fig 1 Photograph showing characteristic posture

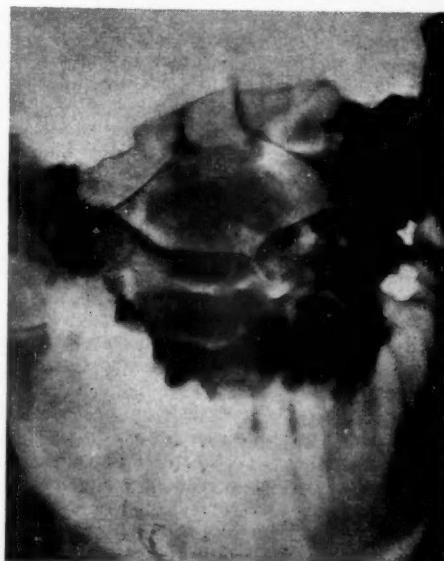


Fig 2 Antero-posterior view through the mouth



Fig 3 Lateral view of atlanto-axial joint

Review of the original X-rays confirmed that the lesion was present then, although not diagnosed. Photographs prior to August 1959 reveal no facial asymmetry.

Discussion

The causes of atlanto-axial subluxation fall into three groups: (1) Those associated with cervical infection in children. (2) Those associated with severe violence. (3) Those in which a subluxation occurs following a sudden unguarded movement of which this is an example; such cases have been reported by Mixter & Osgood (1910), Sudeck (1923), Hess *et al.* (1935) and Cone & Turner (1937), and in all their cases a sudden twisting movement resulted in subluxation.

Treatment in the early stage is by reduction followed by immobilization in plaster of Paris or internal fixation.

The prognosis in the late untreated case is difficult to assess. Corner (1907) considered it to be bad and described cases developing a myelitis going on to paralysis and death. Cone & Turner (1937) quoted a case developing neurological signs sixteen years after the original injury. On the other hand, Hess (1942) and Grogono (1954) both reported late cases without symptoms. In this instance the presence of fixed deformity suggests that fibrous or bony ankylosis has occurred. Direct attack on the atlanto-axial joint would be hazardous and fusion in the position of the deformity would not prevent the increasing

facial asymmetry but might prevent possible future risk of paraplegia.

Failure of a 'ricked neck' to resolve should call for the re-examination of the X-rays and the taking of further pictures if necessary.

I wish to thank Mr T T Stamm for permission to report this case.

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Bone Change in Haemoglobin S-C Disease A G Pollen FRCS

Haemoglobin S-C disease is one of the haemoglobinopathies, a group of related blood disorders in which an abnormal variant of haemoglobin replaces, wholly or in part, the normal haemoglobin. The condition is inherited as a non-sex-linked mendelian dominant, and occurs only in certain members of negro races. Most of the clinical manifestations are due to the presence of haemoglobin S which, when occurring in the homozygous form, is the cause of sickle cell anaemia. Haemoglobin C occurring in the homozygous form produces a mild haemolytic anaemia. Its presence in the heterozygous S-C disease tends to diminish the severity of the haemoglobin S lesions by a dilution effect. Nevertheless after a period of hypoxaemia – whether environmental or the result of some other disease – such patients may develop relatively severe symptoms from infarction of viscera or bone. The diagnosis may be established by electrophoresis, which reveals the abnormal haemoglobins.

Radiological changes in haemoglobin S-C disease may be divided into three groups (Cockshead 1958):

- (1) *Changes associated with erythropoietic marrow hyperplasia*, the result of a chronic haemolytic anaemia. This may be seen as a widening of the medullary cavity of the shafts of the 'short' long bones of the hands, from endosteal bone absorption, and as localized osteoporosis of the ends of the long bones. Widening of the diploë of the skull may occur. Periosteal new bone may be laid down along the shafts of long bones.
- (2) *Changes due to bone infarction*: These lesions occur chiefly in the head of the femur or of the humerus. Radiologically the affected bone becomes flattened and shows some increase in density. In the hip the whole of the femoral head may be involved, the appearance resembling that in Perthes's disease; or an isolated segment may



Fig 1 Left shoulder subluxation, showing ischaemic necrosis of humeral head



Fig 2 Both knees, showing periosteal new bone formation on lower femora

be affected, with localized bone collapse or loose body formation. Similar changes may occur in the humeral head.

(3) *Changes associated with bone infection:* These patients seem peculiarly prone to develop salmonella osteomyelitis and they may show lesions typical of chronic osteomyelitis.

Case Report

A woman, aged 29, a native of Ghana who had lived in Britain for four years, reported in July 1960 with pain and loss of movement of her left shoulder of three weeks' duration. There had been no injury. Radiography revealed an antero-inferior subluxation of the gleno-humeral joint. The humeral head was flattened and showed increased density of the subchondral bone, and rarefaction of the more central part of the head (Fig 1). Further radiographs revealed rarefaction of the tibial condyles, and periosteal thickening of the lower femora (Fig 2). The skull, hips and hands were normal.

Blood investigations: Hæmoglobin 68%. Numerous target cells in peripheral blood. Paper strip electrophoresis revealed the presence of hæmoglobin S and C.

Progress: The patient's shoulder had been reduced on admission, but there was recurrent subluxation, and physical signs suggested a supraspinatus tendon rupture. At exploration the following abnormalities were found: (1) The supraspinatus tendon was degenerate and torn. (2) The synovium was considerably thickened and inflamed. (3) The head of the humerus was crumbling and its articular cartilage was soft and partly shed.

Histological examination showed: (1) Degenerative change of the tendon, with infiltration of basophilic material and absence of collagen fibres. (2) Marked infiltration of the synovium

with acute and chronic inflammatory cells. (3) Areas of dead bone with newly formed osteoid tissue surrounding them. In some places coarse-fibred new bone adjoined the dead bone, and in other areas osteoclastic absorption of dead bone was occurring. The bone changes were compatible with bone infarction followed by a healing process.

Comment: It is tempting to relate the spontaneous rupture of the supraspinatus tendon to an ischaemic episode. It is interesting that this patient travelled from Ghana to Britain by aeroplane, and subsequently spent several weeks in the Austrian mountains on holiday. While there she developed severe pneumonia. She had several possible episodes of hypoxæmia during this period which may have precipitated infarction.

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Spondylolisthesis in a Charcot Spine

D M Riddell FRCS

Charcot's disease of the spine is a relatively common condition accounting for 10% to 15% of Charcot joints in tabetics. Between 4% and 10% of tabetics develop Charcot joints (Cleveland & Wilson 1959). The literature has been reviewed by Thomas (1952), who reported two further cases. Only one report in which a spondylolisthesis was present in association with tabes has been found in the literature. Kronig (1884) described a man of 45 years, a known tabetic in whom the spondylolisthesis was diagnosed clinically, by the shortening of the lumbar spine, and by palpation of the displaced body of the fifth lumbar vertebra, both abdominally and rectally. The remainder of the lumbar spine was unstable but painless.



Fig 1 Spondylolisthesis of the fifth lumbar vertebra

Case Report

A Turkish Cypriot woman, aged 44 years, was found to have syphilis in 1949. Shortly afterwards she developed symptoms of tabes dorsalis. In 1957, following the birth of her second child, she began to complain of low back pain radiating into the right leg. These symptoms slowly worsened and in addition she continued to complain of lightning pains, weakness of both legs and ataxia.

On examination: The lumbar spine was shortened, the ribs descending into the pelvis, and a step could be felt at the lumbosacral junction. Extension and lateral flexion were limited, but she was able to touch her toes easily. Straight leg raising was 110 degrees on both sides. No weakness was found in the lower limbs. The knee and ankle jerks were absent, position and vibration sense were impaired in the legs. The right pupil did not react to light, the left only sluggishly, both pupils reacted sluggishly to accommodation. Romberg's sign was positive.

Investigations: Blood W.R. was negative, but previous positive reactions had been found in the blood and cerebrospinal fluid. The Reiter complement-fixation test was positive.

X-ray (Fig 1) showed a marked spondylolisthesis of the fifth lumbar vertebra on the sacrum. The body of the fifth lumbar vertebra was partially absorbed and there was new bone formation. No defect was present in the pars interarticularis. The left transverse process of the fifth lumbar vertebra was involved in the disease. The remainder of the spine was normal.

Comment

Unfortunately no record was available of the state of her back prior to 1960, and it was impossible to assess the rate of progress of the disease. Careful study of the X-rays showed no defect in the pars interarticularis. It is possible that the evidence for this lesion could have been destroyed by the absorption of bone and formation of new bone, but the cause of the subluxation is almost certainly involvement of the lumbosacral joint by Charcot's disease, and should be classified in Newman's Group IV (1955) in which the subluxation is due to degenerative changes causing facet deficiency.

The patient's symptoms were controlled by a Goldthwait belt.

I am grateful to Mr H Osmond-Clarke for permission to report this patient.

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The following cases were also shown:

Swelling of Tibia in a Boy

Mr G O Tippett

Secondary Carcinomatous Deposits in Bone

Dr R C L Feneley (for Mr G O Tippett)

(An account of this case will be given in a later issue of the *Proceedings*)

(1) Deformity of Right Elbow Following Fracture of the Humerus

(2) Internal Derangement of Right Wrist

Mr W E Tucker

Post-irradiation Fractures of Pelvis

Mr H Piggott

Caffey's Traumatic Lesion in Growing Bone

Dr A Manzoni

(1) Paget's Disease of Right Radius; Goitre and Renal Calculi

(2) Monostotic Paget's Disease Left Tibia (25 Years' History)

Mr H A Kidd

(Meeting to be continued).

Book reviews

The Red Cell

by T A J Prankerd MD

pp ix + 184 illustrated 32s 6d

Oxford: Blackwell Scientific Publications 1961

In his introduction Dr Prankerd gracefully acknowledges his indebtedness to Ponder's monograph 'Haemolysis and Related Phenomena', which was previously the only monograph devoted exclusively to the workings of the red cell. Whereas Ponder sought to explain phenomena largely in terms of physical chemistry and dealt with osmotic forces and the kinetics of haemolysis, Prankerd's approach is predominantly biochemical, although he also devotes chapters to such Ponderian topics as the Hamburger shift and diffusion through the red cell membrane.

After briefly summarizing work on the normal life span of red cells, the author reviews the chemical differences between old and young cells and concludes that metabolism decreases as the cell ages. All known aspects of red cell metabolism are then discussed at length with special reference to glycolytic pathways; red cell enzymes are listed and their functions discussed. It is perhaps a little disappointing that despite rapidly advancing knowledge of the biochemistry of the red cell, we still know so little about the actual metabolic disturbance that characterizes such a condition as hereditary spherocytosis.

In the field of red cell metabolism the author is very much at home and has himself made many useful contributions to knowledge. Those who are familiar with his work will not need to be told that they must buy this book. To others it is warmly recommended as a clearly written account of the subject, containing a great deal of information in a small space.

Cancer. The Significance of Delay

by Robert Sutherland MD DPH

pp ix + 206 + 7 30s

London: Butterworths 1960

It is usually assumed to be axiomatic that the sooner the cancer patient is submitted to appropriate treatment, the better his chances of cure. This book is an unusually penetrating enquiry into the validity of this assumption. The author is the director of the cancer survey conducted under the aegis of the Yorkshire Council of the British Empire Cancer Campaign.

His first problem was to estimate the frequency of delay and its effect on the clinical course and outcome. In this he encountered many major difficulties such as unreliable records, and wide variations in clinical and pathological evaluation,

but above all in the criteria used for 'cure'. In spite of these difficulties he found that delay in procuring radical treatment was alarmingly common and his analysis of its cause goes to the heart of the problem. It is interesting to read that ignorance is probably a minor factor as 'physicians' delay seeking advice as just often as the laity. He concludes that 'earlier treatment may mean life or death to some' and that 'we must do everything we can to ensure that it is given to all'.

To what extent would survival rates be increased if treatment were given immediately the first sign or symptom was noticed? More than three-fifths of the book is devoted to this complex biological problem. There is no doubt that every malignant tumour has intrinsic characteristics which decide its potential malignancy and it may be that, to a widely variable degree, the tissues of every host are capable of defending him against malignant infiltration. On this basis every malignant tumour pursues a predetermined course which it may be impossible to deviate by treatment at any stage. Some growths kill so slowly that they permit life to be continued for years; others kill inevitably soon after discovery, and the majority occupy an intermediate position between these extremes. Dr Sutherland's discussion of this basic problem is lucid, completely free from unwarranted speculation and well documented.

Bleeding Syndromes: A Clinical Manual

by Oscar D Ratnoff MD

American Lecture Series No 421

pp xi + 287 illustrated 68s

Springfield, Ill.: Charles C Thomas

Oxford: Blackwell Scientific Publications 1960

This book gives a clear, contemporary and readable account of bleeding disorders, and is remarkably comprehensive for its size. The author has written for clinicians who are not specialists in coagulation problems so the emphasis is on clinical aspects. No details of laboratory techniques are given but there are adequate introductory chapters on physiology of coagulation and investigation of abnormal bleeding, and a good account is given of laboratory findings in the various conditions. The table of contents and index are easy to use and the book is well documented with 730 references. Although concise the author leaves the reader well aware of unsolved problems in this field.

Readers may regret that there is no mention of Owren's methods for the control of coumarin-like anticoagulants. They may also feel that the value of AHG assay merits more attention than

it gets in the section on haemophiliac bleeding. But this is a useful book for clinicians and students who have some interest in blood coagulation problems, and many clinical pathologists also will find it of value.

Sea Within: The Story of our Body Fluid

by William D Snively Jr MD

pp x+150 illustrated 32s

Philadelphia & Montreal: J B Lippincott

London: Pitman Medical Publishing Co 1960

'Sea Within' is a popular account of body fluid for the general reader in the United States and has evidently been written to satisfy the omnivorous curiosity of the North American laity about physical phenomena of all kinds. There is much interesting information in this book, but like many other popular accounts it is liable to irritate those accustomed to a different style of writing by the looseness of expression, which is so commonly inseparable from a popular account of a scientific subject. Scientific fact, history and crystal-gazing are mixed here in a fascinating way and, provided the intelligent layman can understand what he reads, this must be considered a very good account at his level. Some of the illustrations are good, but others are probably misleading. On the whole this is a good and stimulating book for lay people and may perhaps also fulfil the hope of the author by being of help to physicians, nurses, technicians and dieticians as background reading for technical treatises on body fluid.

Techniques of Thoracotomy

by B T Le Roux MB ChB FRCSE

pp xi+94 illustrated 55s

Edinburgh & London: E & S Livingstone 1961

This is a lucidly written book which meticulously describes the methods used in the Edinburgh Regional Thoracic Unit - and the author pays tribute to Andrew Logan as the originator of the technique in that unit - from which all surgeons could learn something.

In the main the methods used are acceptable by any unit engaged in such major surgery in Great Britain; but where such minutiae as the folding of towels are described, there will, of course, be many differences to be found. Most surgeons would not agree that the use of diathermy does not make for a more rapid entry of the chest, nor would they accept that the anaesthetic method to be used should forbid its use. The colour illustrations indicate how much more restful are dark-coloured drapes and towels. In the many colour photographs it is often difficult to discern (even by the experienced thoracotomist) the structures mentioned, and they illustrate how much preferable is a good line drawing in such an anatomical text.

The details covered are those normally learnt by apprenticeship in a working unit, and are much more easily seen than described. The present need for such a book on basic technique underlines the thesis that all general surgical trainees should spend a short time with such a major specialist unit.

Quantitative Cellular Haematology

by J M Yoffey DSC MD FRCS

American Lecture Series No 412

pp xv+122 illustrated 44s

Springfield, Ill.: Charles C Thomas

Oxford: Blackwell Scientific Publications Ltd 1960

This one hundred page monograph with its bibliography is a quite excellent review of the current debate on 'the lymphoid complex'. It is not complete, nor can it be so, for the debate is still in progress. None the less it is a well-timed publication and Professor Yoffey is one of the pioneers to recognize the fundamental importance of a quantitative dynamic approach to diagnostic haematology: the philosophy expressed throughout this monograph represents the attitude which all modern haematologists should accept. A great deal of reference is made to animal experimental work and one is always left with frustration that much of this cannot be applied to the human physiological story, yet it represents information and a method of scientific approach which must be understood by all those attempting the study and interpretation of morphological changes in haematology.

Although many would not accept a similar potential for the small lymphocyte, the position in the pattern of life of the large lymphocyte with its totipotential or pluripotential qualities is becoming a little clearer. The interchange between plasma cell, histiocyte, large lymphocyte and circulating macrophage, spotlighted by human reaction to such diseases as infective mononucleosis, demonstrates the protean nature of this member of the reticulo-endothelial system. The more recent realization that normal peripheral circulating cells, almost certainly the large lymphocyte, can enter into mitosis in culture appears to confirm this. Experience with marrow ablation by chemotherapeutic means and subsequent replacement by homologous transplants, demonstrates the importance of the large lymphocyte as a stem cell still capable of lateral development for the initiation of an immune response.

Professor Yoffey's monograph covers all phases of the lymphocyte's natural history, and reviews and analyses the various interpretations placed upon morphological change. Perhaps it is best read in conjunction with the more recent surveys of this aspect of reticulo-endothelial activity by Medawar and Burnet.

Occupational Therapy in Rehabilitation
edited by E M Macdonald B Litt TMAOT
pp xvi + 348 illustrated 37s 6d
London: Baillière, Tindall & Cox 1960

Although this is a good book it is also a disappointing one. In Great Britain we are fortunate in having some of the best occupational therapists in the world, and several of these have joined in writing sections of Miss Macdonald's book. It is this that makes the book a good one, as respect for the authors makes one read with interest what they have to say about their favourite topics. The weakness of the book is in the way it is organized. The amount of overlap is excessive and consequently many of the sections are far too brief - half a page on peripheral nerve injuries and even less on the treatment of spastic paralysis in cerebral palsy cannot do justice to the occupational therapy of these conditions.

This book can be recommended as a sincere attempt to show how useful occupational therapy can be, but one must expect tantalizing brevity in many sections.

Pages in the History of Chest Surgery

by Rudolf Nissen MD and

Roger H L Wilson MB BChir
pp viii + 166 illustrated 60s

Springfield, Ill.: Charles C Thomas

Oxford: Blackwell Scientific Publications 1960

The earlier efforts of the thoracic surgeon were concerned largely with the eradication of disease without disaster; attention was focused mainly upon anatomical and pathological problems. Nowadays attention is concentrated on maximal restoration of physiological function. The opportunities for advancing knowledge from the study of physiological problems in the heart and lungs are immense and are now being actively explored.

The student of thoracic surgery should know the background of his specialty but few of them have ready access to the pioneer work of those famous predecessors whose efforts did so much to put the specialty where it is to-day.

The authors present the story of thoracic and cardiac surgery in a novel and readable form. The story is built around photostat copies of the original articles or case reports together with biographical notes and photographs of the men concerned. In this way one can sense the enormity of problems which now seem commonplace.

It is therefore fortunate that the authors consider in some detail many of those features of thoracic surgery which to-day are generally regarded as being solved - problems such as that of the open pneumothorax, the actual thoracotomy and the development of the details of pulmonary resection. Less emphasis and detailed description

is given to the more recent developments, particularly in cardiac surgery, which are still fresh in our minds.

The book is a pleasant history of thoracic surgery presented in an interesting and arresting manner. But it is more than this - in underlining the change from the anatomical to the physiological and functional viewpoint, the authors hope to see thoracic surgery 'leading surgery as a whole to new triumphs through changing viewpoints'.

Blood Diseases of Infancy and Childhood

by Carl H Smith MA MD

pp 572 illustrated 127s 6d

St Louis: The C V Mosby Company

London: Henry Kimpton 1960

The writing of this book, by an experienced American paediatrician, illustrates the current awareness of the importance of blood diseases in paediatrics. Its early chapters, dealing for example with blood changes resulting from growth, blood dyscrasias resulting from maternal-fetal interaction, blood transfusion, the differential diagnosis of jaundice in the neonatal period, erythroblastosis foetalis, iron-deficiency anaemia and the megaloblastic anaemias, satisfactorily fulfil the avowed aim of presenting the essential and distinctive features of blood diseases in infancy and childhood. The remainder of the book, almost two-thirds of it, corresponds more closely with an orthodox comprehensive textbook of haematology. This is no doubt the consequence of the dilemma in which an author, attempting to describe the blood diseases of infancy and childhood, must inevitably find himself. What is he to omit, bearing in mind that almost every blood disease has occurred in this age group at one time or another?

Dr Smith has opted for comprehensiveness, but it is not always clear from his descriptions whether he is referring to a disease as it occurs commonly in adults or to the rare and isolated cases which have been reported in children. The short section on Cyclic Thrombocytopenic Purpura Related to the Menstrual Cycle (p 518) has presumably crept into the book by mistake, but in at least one place dangerous ambiguity has arisen. In referring to the treatment of chronic myelocytic leukaemia, busulphan (Myleran) is mentioned, and although it is pointed out that the amount given must be 'individualized', especially in children, the usual daily doses are stated to be 4 mg, or even 6 mg. These are doses which are normally given to adults and are far too high to be given with safety to children.

The difficulty as to what to include or what not to include emphasizes that although blood diseases in childhood present some particular problems - and there are of course some important disorders

peculiar to the neonatal period - these differences should not be over-emphasized. The separation of 'paediatric haematology' from 'adult haematology' seems both unnecessary and undesirable, and as the present book illustrates, is difficult to achieve in practice. The book is however, well produced, authoritative, and up to date.

Electron Microscopy in Anatomy: Proceedings of a Symposium held by the Anatomical Society of Great Britain on the Ultra-structure of Cells

pp viii + 288 illustrated 50s
London: Edward Arnold 1961

This volume is the proceedings of a Symposium held in London in April 1959. The electron microscope has opened up a new field for the investigations of biological problems. In the present volume twenty chapters are devoted to various aspects of electron microscopy. These range from 'present and future possibilities of electron microscopy' to 'the secretory process of the pancreatic exocrine cell'. All of the chapters are of interest to the biologist, histologist, anatomist and pathologist. The book can be recommended without reservation.

A Textbook of Clinical Pathology

edited by Seward E Miller MD
6th ed pp xxi + 894 illustrated £6
London: Baillière, Tindall & Cox 1960

This book was first published in 1938 'to give the medical student, intern, resident physician, clinical pathologist and teacher of medicine an authoritative source of information on how most advantageously to use the clinical laboratory'. It has succeeded very well in achieving its aim; if more doctors used this book, the hospital laboratory would be employed much more intelligently and much useless work would be avoided.

The main criticism is one of balance: with increasing development of clinical chemistry hospital staff need more guidance in the use of the laboratory in this field than in haematology, but there are nearly twice as many pages dealing with the latter than with the former.

In a book with the aims quoted above, and which does not set out to be a laboratory bench textbook, space could be more profitably used in further discussion of when to use, and equally important, when not to ask for various tests, rather than in the details of technique, as given in the haematology and virology sections. The articles on interpretation of ketosteroids and corticoids are inadequate for clinical guidance, but could be made very much more valuable without increase in length if the space used for description of methods was given to interpretation and the same comment applies in a number of other

places. In a book such as this, no details of technique should be given other than those needed by the doctor to ensure that proper specimens are taken at the proper times.

Nevertheless, this is an excellent work, which could be read with advantage by those to whom it is addressed: those who use it will get much more assistance in their clinical problems without increasing the total load on the laboratory.

The Use of Isotopes in Haematology

by L G Lajtha MD DPhil
pp x + 83 illustrated 21s
Oxford: Blackwell Scientific Publications 1961

This book describes the application of radio-isotope techniques to haematology. It covers all the most widely used methods and is a useful synopsis of the subject. There is an adequate bibliography so that reference may be made to original articles for more detailed study. The short chapter on autoradiography illustrated by some of the author's own photographs of individual labelled cells is perhaps the best feature of the book. There is a very useful table as an appendix, giving the radiation doses received in the tracer tests described.

It is regrettable that the lettering in the diagrams has not been standardized. In some figures it is outstandingly bad. More care might also have been taken in editing the text. With these reservations, however, this book can be recommended as a concise introduction to the subject.

Survey of Research in Gestation and the Developmental Sciences

by Jack Davies MA BSC MD
pp v + 203 48s
London: Baillière, Tindall & Cox 1960

The author states that his book is a review based on an analysis of work supported by Federal and private agencies in the United States and is published with the co-operation of the Association for the Aid of Crippled Children. The review is selective and by no means exhaustive on any topic, and the author bluntly admits that his own interests have often attracted his attention more than subjects on which he has not worked.

One of the most interesting chapters is on the special and general physiology of the fetus and is concerned with matters such as the baby's first breath, changes in the vascular system at birth and activities of fetal endocrinies. The book cannot fail to be of interest to paediatricians and obstetricians, but it is doubtful whether the general reader will recall enough anatomy, physiology and particularly biochemistry to allow him to follow the subtleties of argument in the author's

'non-technical' terms. The book, admirable in its intentions, falls between two groups of readers – the experts and those less expert but wishing to educate themselves in recent research in a particular field. The task of the latter is made the tougher by the complete lack of an index and any edifying illustrations. As the expert will go to more thorough sources of information, such as the latest edition of Marshall's 'Physiology of Reproduction', one cannot help wondering what is the purpose of this volume. If it is to justify to the non-expert the giving of grants to workers in the field of developmental biology then its language is ill-chosen, if for the expert it is too superficial. One can only assume that some national or intellectually parochial objective has stirred Professor Jack Davies to spend his time compiling these reviews. Yet the book does contain much interesting and valuable information for certain people.

Bulletin of the Medical Library Association

Vol 49 No 1 Part 2 of two parts

The National Library of Medicine Index Mechanization Project July 1, 1958 – June 30, 1960
pp 96 illustrated

Washington, D.C.: National Library of Medicine 1961

The name 'Index Medicus' is often used familiarly, but not always entirely accurately, for a series of indexes, all of American origin, to the contents of medical journals.

It was, however, the exact title of the first of those indexes, produced by J S Billings at the Library of the Office of the Surgeon-General of the U.S. Army. Now, the successor of that library, the National Library of Medicine, is producing monthly the new 'Index Medicus'. This special issue of the *Bulletin of the Medical Library Association* is an account of the studies undertaken to establish the form of the new 'Index Medicus' and the methods, and the mechanization of some of them, used in its production.

It is a sober and factual account of the work behind a publication which is taken wholly for granted in medical libraries all over the world; which is probably more frequently handled than any other single publication in them and which only arouses comment when it does not supply the information sought.

The reader will not only be moved to admiration of the work recorded: he will also be likely to find himself using the 'Index Medicus' more effectively.

The support of the Council on Library Resources made the project a possibility; the devotion of a band of people who had many other responsibilities which were never put aside, made it a reality. It is indeed noteworthy that during the

whole period of preparation for the new 'Index Medicus' the administration of the project was only one of the tasks of the Director of the National Library of Medicine, Dr Frank B Rogers; and that Mr Seymour Taime was not only the principal investigator, but also the head of the Index Division of the National Library of Medicine which throughout this strenuous period maintained publication of the 'Current List of Medical Literature'.

Indeed, the only criticism of this admirable report is that it gives no greater prominence to those two names than a modestly hidden comment at the end of the preface.

Electron Microscopy. A Handbook for Biologists

E H Mercer DSC PhD and M S C Birbeck MA
pp vi + 76 9s 6d

Oxford: Blackwell Scientific Publications 1961

The authors have aimed to throw light on the technical problems which face the biologist in preparing his material for electron microscopy and therefore a more modest but informative title would have better befit this little book.

In describing selected techniques for the fixation, dehydration, embedding and sectioning of biological specimens, the handbook has a definite limited value from the practical point of view. In many ways the work is not full enough to meet more than the initial demands of a would-be electron microscopist and through a number of its pages it lacks a balanced presentation of differing points of view. However, the book has an essentially practical merit and must therefore be judged as a guide on the laboratory bench.

Sufficient emphasis has not been placed on the different reactions of various tissues to fixation and embedding. In consequence the instructions are inadequate in dealing with the required variations of technique in treating, for example, hard and soft, adult and embryonic tissues. The paragraph on microtomy is useful as far as it goes, but it does not grapple with some of the most wearisome of the technical problems of thin sectioning. For example, although a method of preparing glass knives is described and illustrated, no help is given on the means of assessing the worth of the cutting edges of these knives.

Two of the major problems of microtomy – chatter and compression – have not been fully treated, particularly as regards their bearing on such matters as the hardness of embedding medium and specimen and the speed of cutting.

The paragraphs on preparing and supporting serial sections are particularly valuable as are the various recommendations on photography. There is moreover much useful information on materials and formulae which forms an excellent appendix to the book.

Treatment of Urinary Lithiasis

edited by Arthur J Butt BS MD FACS

pp xxii + 577 illustrated £8 8s

*Springfield, Ill.: Charles C Thomas**Oxford: Blackwell Scientific Publications 1960*

A comprehensive work needs many authors. The views of thirty-two contributors on the treatment of urinary stone are collected in this impressive volume. They fall into three overlapping aspects: historical, scientific and practical. The story of stone is one of the most fascinating in medical history and the editor himself does it full justice. The biochemical side is fully covered and there can be few points which are not considered. From the practical surgical point of view all that is included is excellent, but there are some important omissions. In particular, there is no mention of partial nephrectomy, a procedure in wide use in this country as a prevention of recurrence of stones in the lower calyx. There is no specific reference to medullary sponge kidney, although the congenital cystic dilatation of the renal collecting tubules described by Vermooten is probably the same. There are, however, chapters on coagulum pyelolithotomy, on the instillation of stone 'solvents' and on ultrasonic disintegration of stones with no danger of 'neoplastogenesis'. For renal surgery the classical loin approach is preferred to the more adequate exposure through the bed of the excised rib.

Perhaps the best chapters are those dealing with the medical management of the disease and they should provide much food for thought and action for physicians and surgeons.

Die Intersexualität

by Prof Dr Claus Overzier

pp xv + 560 illustrated DM 119

Stuttgart: Georg Thieme Verlag 1961

This extremely well-produced book on Intersexuality in Man, written in German, comprises a collection of what might be termed miniature monographs on many aspects of this subject. The eighteen contributors, drawn from a wide international field, have written on topics of their own particular interest and experience.

The contribution by Dr C E Ford on the cytogenesis of intersexuality and that of Dr H Gelbke on plastic operations are of particular interest, the first for its lucid account of the clinical manifestations of chromosomal anomalies, the second for a description of the ingenious surgical procedures that are now possible for cases of intersex. It is well to remember, however, as indeed Dr Gelbke hastens to point out, that (as yet) intersex is a biological phenomenon and not legally recognized. The inclusion of a chapter on transvestism (Dr J H Schultz) and reference to the problems

of homosexuality reflect the wide scope and the progressive outlook of this work.

Each chapter includes an historical review as well as the diagnostic features, treatment and prognosis of the syndrome discussed, and concludes with a comprehensive and up-to-date bibliography.

The general production of the book is excellent and the photographs and diagrams are clear and helpful.

The following books have also been submitted for review:

Casson F R C

Common nervous disorders

pp 88 4s

*London: W & G Foyle 1961***De Lestapis S**

Family planning and modern problems:

A Catholic analysis

pp xx + 326 30s

*London: Burns & Oates 1961***Imperati L & Tommaseo T**

Chirurgia delle arterie mesenteriche

pp 195 illustrated L 4.800

*Roma: Edizioni Mediche e Scientifiche 1960***Marti-Ibáñez F**

A prelude to medical history

pp 253 \$5.75

*New York: MD Publications Inc 1961***Martindale**

The extra pharmacopœia

Supplement 1961 to Vol II 23rd ed 1955 and Vol I

24th ed 1958

pp xii + 315 32s 6d

*London: The Pharmaceutical Press 1961***Morris A C Jr**

A physician's introduction to electronics

pp 43 illustrated 15s

*Oxford, etc.: Pergamon Press 1961***Potter J M**

The practical management of head injuries

pp xii + 84 12s

*London: Lloyd-Luke 1961***Safar P & McMahon M C**

Resuscitation of the unconscious victim

2nd ed pp xi + 87 illustrated 16s

*Springfield, Ill.: Charles C Thomas**Oxford: Blackwell Scientific Publications 1961*

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